

## Medical Officer's (MO's) Memorandum: Tracked Safety Issue (TSI)

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**Subject:** Postmarketing Reports of Melanoma in Viagra Users

**TSI:** TSI #1579

**Date of Activation:** February 18, 2016

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## 1. Executive Summary

In April 2014, Li et al<sup>1</sup> published an article in JAMA International describing the results of an epidemiology study that evaluated a possible association between sildenafil citrate and melanoma in US men. In 2015, DBRUP became aware of an increasing number of postmarketing adverse event (AE) reports of melanoma in Viagra (sildenafil citrate) users. The majority of these reports came from lawyers. In October 2015, the Office of Regulatory Policy (ORP) received a Freedom of Information Act (FOIA) request to provide any documents related

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<sup>1</sup> Li, Qureshi, Robinson, Han, JAMA International, Published online April 7, 2014, pages E1 –E7

to FDA's possible consideration of adding language to the Viagra label concerning melanoma or skin cancer. In February 2016, in response to a still increasing number of postmarketing AE reports of melanoma in Viagra users (still mostly from lawyers), and in collaboration with the Office of Surveillance and Epidemiology (OSE), the Division determined that the issue should be further investigated as a Tracked Safety Issue (TSI). TSI #1571 was opened.

To initiate TSI#1579, the Division of Pharmacovigilance II (DPVII) was asked to identify all postmarketing reports of melanoma in users of the PDE5 inhibitors (PDE5i) sildenafil, tadalafil, vardenafil and avanafil. DPVII identified a total of 130 cases in FAERS for the years 2011 to 2015 inclusive. A principal objective of this memorandum is to describe the Clinical analysis of these 130 cases.

In summary, for the original 130 cases, most reports do not contain medical history or clinical detail on confounding conditions, such as sun exposure, complexion type, etc. There is no working definition to make the determination of a drug-related event relative to melanoma occurrence. Data is inadequate to inform dose and time response analysis. In many reports, the time of the melanoma event is either unknown, or remote from the time of reporting, a further potential confounding factor. In most cases, there is scant information to define the tumor including tumor stage, grade and pathology of the excised lesion. Treatment outcome is also not well described in the majority of cases.

One role of FAERS is to detect rare adverse events associated with drugs that were not detected during drug trials. Events with a long lag time between drug use and event occurrence may be confounded by other factors. One factor apparent in these 130 cases appears to be solicited reporting. The majority of cases do not have enough information about risk factors, duration of therapy, patient history, and concomitant medications to make a correlation between drug and event. The patients who receive PDE5i are generally older men who have erectile dysfunction and may already be at higher risk for melanoma independent of PDE5i use.

Finally, in the absence of a known accurate denominator of patients exposed to various PDE5 inhibitors, it is difficult to assess incidence of melanoma as greater than background.

On June 15, 2016, an information request was sent to Pfizer, Lilly, Bayer and Vivus; the Sponsors of currently approved PDE5i drugs. This request contained a series of analyses to be performed on their respective PDE5i safety databases to detect a disproportional incidence of melanoma in patients exposed to PDE5i, if one existed. DBRUP agrees with the Sponsors' opinions that the clinical trial and post marketing data overall do not indicate a melanoma signal.

In their consultative review, DPVII identified 203 cases of melanoma in patients receiving a PDE5i, of which 190 reported sildenafil use; 93 out of 95 cases with a documented reason for use reported erectile dysfunction as the indication. Because of a lack of documented PDE5i dose information in the case series, DPVII was unable to comment on a dose-response relationship. Furthermore, the cases lacked documentation of melanoma risk factors, such as genetic and lifestyle factors that may play a role in the onset of melanoma. It was noted a large proportion of the 203 cases were reported by lawyers (n=174), and a few by consumers (n=5), in response to class action lawsuits that followed the Li et al. publication. Further, DPVII noted that despite

chronic and more frequent dosing, there was only one identified case of melanoma in situ in a female patient taking a PDE5i for the treatment of pulmonary arterial hypertension (PAH). Considering the intermittent (and therefore inconsistent) exposure of PDE5i in the treatment of ED, the long onset latency of melanoma, and insufficient data quality in the FAERS cases, DPVII was unable to draw any causal inference from their analysis.

In their consultative review, the Division of Oncologic Products stated, “In conclusion, based upon the information provided and the currently available data sources, there is no definitive signal from the clinical oncology perspective that suggests a causal relationship between administration of PDE5Is and melanoma.”

In their memorandum, the DBRUP Pharmacology/Toxicology review team concluded, “There is no definitive evidence indicating that PDE5 inhibitors could promote melanoma development in human melanoma cells.” They recommended “...additional studies to provide further insights into the PDE 5 inhibitor role, if any, in melanoma development; but these studies may not provide a causal link as there are currently too many variables to define the role of PDE5 inhibitors in melanoma formation.” In an April 5, 2017 Addendum, Pharmacology/Toxicology clarified “...the Nonclinical Team does not recommend new nonclinical studies, and pharmacovigilance is the most appropriate method to monitor potential melanoma development in PDE 5 inhibitor users.”

At the current time the data are insufficient to allow the conclusion that there is a causal association between Viagra or PDE5i use and the occurrence of melanoma.

At this time, the Clinical team recommends continued pharmacovigilance.

## 2. Regulatory Background

In April 2014, an article published in JAMA Internal Medicine<sup>2</sup> described the results of a prospective cohort study evaluating the possible association between sildenafil use for ED and risk of melanoma among US men. The study biennially investigated the incidence of melanoma, squamous cell cancer (SCC) and basal cell epithelioma (BCE). According to the authors, recent use of sildenafil at baseline (2000) was associated with an increased risk of subsequent melanoma with a multivariate-adjusted hazard ratio of 1.84 (95% CI, 1.04-3.22). Increased risk for SCC or BCE was not observed.

In 2015, DBRUP became aware of an increasing number of postmarketing adverse event (AE) reports of melanoma in Viagra users. Most of the reports were from lawyers.

In October 2015, ORP received a FOIA request to provide any documents related to FDA consideration of adding language to the Viagra label concerning melanoma or skin cancer.

In February 2016, in response to still increasing numbers of melanoma AE reports (still mostly from lawyers), OSE and DBRUP decided to open TSI #1571 to investigate the issue. DPVII was

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<sup>2</sup> Li, Qureshi, Robinson, Han, JAMA International, Published online April 7, 2014, pages E1 –E7

asked to identify all postmarketing reports of melanoma in users of the PDE5i products, sildenafil, tadalafil, vardenafil and avanafil. A total of 130 cases were identified in FAERS for the years 2011 to 2015. This memorandum will include a Clinical discussion of 1) the 130 original cases, 2) the Sponsors' submissions of additional clinical trial and postmarketing information, and 3) the conclusions and recommendations from other disciplines, including consultants.

### 3. Materials Reviewed

1. 130 Medwatch Reports (2011-2015) – AE reports of melanoma in users of PDE5i
2. Publications:
  - a. Li, Qureshi, Robinson, Han et al: Sildenafil Use and Increased Risk of Incident Melanoma in US Men, JAMA International, Published online April 7, 2014, pages E1 –E7
  - b. Loeb, Folkvaljon, Lambe; et al: Use of Phosphodiesterase Type 5 Inhibitors for Erectile Dysfunction and Risk of Malignant Melanoma, JAMA 2015; 313: 2449-55.
3. Post-Approval Safety Update Report for NDA 21368 (tadalafil): April 16, 2014 to October 15, 2014
4. European Medicines Agency Report: Pharmacovigilance Risk Assessment Committee (PRAC) dated November 6, 2014 (EMA/PRAC/631153/2014)
5. Sponsors' Responses to DBRUP Information Requests to characterize the incidence of melanoma in the PDE5i clinical studies.
6. Reviews/Consults from Other Disciplines and Divisions:
  - a. OSE DEPIII (Epidemiology) Reviews: March 4, 2015 and April 27, 2016
  - b. OSE DPVII (Pharmacovigilance) Review
  - c. OSE DEPIII (Drug Utilization) Review
  - d. DBRUP Pharmacology/Toxicology Review
  - e. Division of Oncology Products (DOP) Consultative Review

### 4. Clinical Review

#### 4.1 Clinical Background

It is projected that by 2015, 322 million men worldwide will be affected by erectile dysfunction (ED) {BJU Int., 1999;84(1): page 50}. PDE5i are the most commonly prescribed medications used to treat ED.

In a July 12, 2016, review, DEPII estimated that 4.7 million PDE5i prescriptions were issued in the U.S. for the one year period ending February 2016. The vast majority of patients to whom PDE5i were prescribed had ED as the primary diagnosis and were older than 40 years of age. A total of 428,000 sildenafil prescriptions were issued for the treatment chronic pulmonary diseases, which includes PAH. PDE5i are also prescribed to a small number of pediatric PAH patients. Approximately 104 million PDE5i prescriptions were dispensed between March 2010

and February 2016, 49 million (47%) of which were for sildenafil and 44 million (43%) were for tadalafil. 882,000 of the tadalafil prescriptions were for the treatment of BPH.

Melanoma skin cancer incidence varies significantly by race with light skinned persons having the highest incidence rates. Known risk factors include: ultraviolet (UV) light/sun exposure, history of sunburns, and being light skinned or of the Caucasian race. The incidence and prevalence of melanoma in patients with ED, BPH or PAH is not readily available in the literature.

Research in England (1990-2010) suggests that incidence rates of melanoma on the trunk and upper limbs are increasing. Incidence rates vary by age, and have increased in older men (60+ years) as compared to in younger men (less than 60 years). The incidence of melanoma also varies by ethnicity: in white, non-Hispanic US males the incidence was 24.6 per 100,000 per year, for white, Hispanic males it was 4.2 per 100,000 per year, and for black males it was 1.0 per 100,000 per year in 2011.<sup>3</sup> The site-specific incidence of melanoma varies according to age. The incidence of melanoma localized to the trunk and the lower extremity decreases with advancing age. A significant increase of melanoma localized on head and neck areas can be found in older patients. Only 0.2% of melanomas occur in the genital region. Nearly 80% of melanomas in patients aged 80 years and older were found in the head and neck areas. Melanomas developing at different body sites are associated with distinct patterns of sun exposure. Melanomas of the head and neck are associated with ongoing patterns of sun exposure, whereas trunk melanomas are associated with intermittent patterns of sun exposure which may support the hypothesis that melanomas may arise through divergent causal pathways.<sup>4</sup>

The incidence of non-melanoma skin cancer (NMSC) is highest in light skinned persons. Known risk factors include: UV light/sun exposure (particularly chronic/long term) and being light skinned or of the Caucasian race. No association with NMSC and PDE5i use has been observed. The risk of NMSC in patients with BPH or PAH is not reported in the literature.

The table below lists the currently available PDE5i drugs in the US market:

**Table 1: FDA-Approved (Branded) PDE5i Currently Marketed in the United States**

Trade Name	Indication	PDE5i Sponsor	Generic Name	Route(s) of Administration	NDA	Year of Approval
Viagra	ED	Pfizer	sildenafil	oral prn	020895	1998
Cialis	ED	Lilly	tadalafil	oral prn, daily	021368	2003
	BPH			oral daily		2011
	ED/BPH			oral daily		2011
Levitra	ED	Bayer	vardenafil	oral prn	021400	2012
Staxyn	ED	Bayer	vardenafil	orally disintegrating prn	200179	2010

<sup>3</sup> CDC Morbidity and Mortality Weekly Report (MMWR): 2015: 63(21), pages 591-596.

<sup>4</sup> Garbe C and Leiter U, 2009, Clinics in Dermatology 2009:27: pages 3-9.

Stendra	ED	Vivus	avanafil	oral prn	202276	2012
Revatio	PAH	Pfizer	sildenafil	oral daily	021845	2005
				suspension	203109	2012
				intravenous	022473	2009
Adcirca	PAH	Lilly	tadalafil	oral daily	022332	2009

## 4.2 Review of Epidemiology Literature

In the literature, medical comorbidities have been reported as being associated with an increased risk of melanoma:

1. A personal history of prostate cancer is associated with an increased risk of melanoma, which the authors conclude may not be entirely a result of greater medical scrutiny.<sup>5</sup> In the same article, the authors state that they did not find an altered risk of melanoma associated with a personal history of other cancers.

*Reviewer's Comment: This analysis is derived is from of the Health Care Professionals Follow-up Study and should be regarded as hypothesis-generating, not as conclusive. Of note, the available details in the 130 melanoma cases did not show evidence for a personal history of prostate cancer.*

2. In another study, 1882 patients with ED were followed for 5 years and compared to a cohort of 9,410 randomly selected patients who visited the same ambulatory care center in Taiwan.<sup>6</sup> A medical history of any cancer excluded patients from the study. The hazard ratio of having any cancer was 1.42 for ED patients as compared to the control patients. The types of cancer sampled in the 5-year period for ED patients included oral (n=4, 9.3%), gastrointestinal (n=15, 34.9%), respiratory (n=4, 9.3%) and other types (n=10, 23.3%), which included melanoma - but N and % were not specifically stated for melanoma. After analyzing the risk of smoking-related cancers among the sampled patients, the authors found no significant difference in the adjusted hazard ratio of such cancers during the 5 year follow-up period between the two cohorts. It is the author's opinion that smoking may be a significant confounder for the relationship between ED and increased risk of cancer. With regression modeling, the authors found that ED patients were still more likely to have cancer than comparison patients. Of note, the authors feel that PDE5i may actually be of benefit in reducing inflammation and associated conditions such as cancer and therefore they regard PDE5i as beneficial, not as averse.

*Reviewer's Comment: This small study raises the question whether ED itself is associated with an increase in cancer incidence. This small sample will need a larger study to confirm the author's conclusion. Identifying smoking as confounder also raises the question of latent variable(s) regarding melanoma causality. There are numerous studies documenting a relationship between smoking and melanoma incidence.*

<sup>5</sup> Li, Qureshi, Ma, et. al., Journal of Clinical Oncology, 2013: 31(35)4394-4399.

<sup>6</sup> Chung, Kang, Liao, Chiu, Lin, Journal of Sexual Medicine 2011: 8: 1513-1520

Two highly relevant epidemiologic publications on melanoma and PDE5i are:

1. **The cohort analysis study conducted by Li et al<sup>7</sup> from the Health Professionals Follow-up Study, published April 2014 in the online Journal of the American Medical Association.** This publication preceded the spur in reports of melanoma in PDE5i users.

*Reviewer's Comment: The reader is referred to the detailed review of this publication by the Division of Epidemiology (DEPI) in the Office of Surveillance and Epidemiology (OSE).*

The Health Professionals Follow-up Study was a prospective cohort study of 51,529 U.S. men who in 1986 completed a baseline questionnaire related to health and personal habits, including diet. Initially, men aged 40 to 75 years of age completed this baseline questionnaire that collected information on age, marital status, height, weight, ancestry, disease history, physical activity, smoking habits, and diet. This prospective study was intended to assess the effect of dietary fat on prostate cancer. Follow-up was initiated after completion of the baseline questionnaire. Subjects were mailed biennial questionnaires. The response rate exceeded 90% in the follow-up.

Since 1986, participants were instructed to report diagnosis of melanoma, squamous cell cancer (SCC) and basal cell cancers (BCC) on the biennial surveys. Only pathologically confirmed invasive cases of melanoma or SCC were documented as outcomes.

Beginning in 2000, participants were also queried as to whether in the past three months they had undergone treatment to help with erection problems, including treatment with oral sildenafil (the only PDE5i available in the U.S. at the time), penile injections, vacuum erection device, etc. The patients were also asked whether they had ever received a treatment for ED before, including sildenafil. No information on the dose or frequency of sildenafil was collected. The stated motivation for this particular study modification was the report of an *in vitro* study suggesting that PDE5 inhibition might increase invasiveness of early stage melanoma.<sup>8</sup> The authors of the *in vitro* study stated that the *in vitro* data suggested that the effect is present only in cells with BRAF mutations. In cells with that mutation, PDE5 activity is usually already down regulated. On the other hand, the authors stated, there have been reports that sildenafil has anti-tumor effects.

*Reviewer's Comment: The in vitro data are unclear as to the effect of sildenafil on melanoma.*

In one analysis, the 2000 questionnaire in the Health Professionals Follow-up Study served as the baseline population. Patients with any cancers at baseline were excluded. Sildenafil use at baseline (in the past 3 months, which began to be reported in 2000) was the main exposure of interest. The patients were surveyed biennially from 2000 to 2010 for the

<sup>7</sup> Li, Qureshi, Robinson, Han, op. cit.

<sup>8</sup> Arozarena, Sanchez-Laorden, Packer, Hidalgo-Carcedo, Hayward, Viros, Sahai, Marais, 2011, Cancer cell, 19(1): 45-57.

diagnosis of melanoma. No information on the dose or frequency of sildenafil use was collected at baseline or during follow-up. The report contains no analysis regarding the use of other PDE5i drugs in the study population.

This study required the pathologic verification of the melanoma diagnosis but not pathologic verification of BCE or SCC. For the primary analysis, patients with other cancer diagnosis were excluded. Also excluded at baseline were users of other therapies (other than sildenafil) as well as non-White patients. Only invasive melanoma cases were considered for analysis. Lag analysis was performed by excluding cases occurring in the first follow-up period (2000-2002). Men who used sildenafil but did not report sexual dysfunction were excluded.

Li et al also performed sensitivity and secondary analyses:

- Hazard ratios were estimated for ‘ever use’ that included recent use, e.g., 3 months before, and use at other times
- Excluded from the study analysis were men with cardiovascular disease, type 2 diabetes mellitus, or hypertension on baseline analysis, as an attempt to eliminate confounding by health status.
- Sildenafil users who had used other therapeutic options for ED were excluded to eliminate confounding by other ED therapies.
- To assess the confounding by erectile function, the overall erectile function was assessed and graded to see if this was associated with the risk of subsequent skin cancers.
- Time lag analysis was conducted to clarify the temporal relationship between sildenafil use and the occurrence of skin cancers occurring in the first follow-up period (2000-2002).
- The investigators also sought to clarify the association of sildenafil use with other cancers, including all non-skin cancers as well as major individual non-skin cancers, with adjustments for age, BMI, smoking, physical activity, UV index at birth, and at ages 15 and 30 years, multivitamin use, physical examination in the last years and other ED treatments.

The results of this analysis were reported online in JAMA Internal Medicine on April 17, 2014. For the 25,848 participants in the analysis, a total of 580 SCC and 3030 BCC cases were reported. 142 participants were reported with melanoma. Of these 142 participants, 14 reported sildenafil use and 128 reported no sildenafil use. 27.1% of the total 25,848 patients reported no sildenafil use and 61.5% of 25,848 patients reported recent sildenafil use. After adjusting for factors, including mole count, family history, hair color, and sun exposure, the authors concluded that men with a history of recent sildenafil use, e.g., ever use, had an increased risk of melanoma compared to men who reported that they had never taken sildenafil, with a multivariate-adjusted hazard ratio (HR) of 1.84 (95% CI, 1.04-3.22). There was not an increase in the hazard ratio for SCC or BCC.

To summarize, the results from the primary analysis were:

- Recent sildenafil use at baseline was associated with an increased risk of subsequent invasive melanoma with an adjusted HR of 1.84 (95% CI, 1.04-3.22).

- An association between sildenafil and squamous cell carcinoma (SCC) (adjusted HR: 0.84, 95% CI, 0.59-1.20) or basal cell carcinoma (BCC) (adjusted HR: 1.08, 95% CI, 0.93-1.25) was not reported.

The results from the secondary analyses were:

- “Ever use” of sildenafil was associated with a greater risk of invasive melanoma compared to no previous use (HR, 1.92; 95% CI, 1.14-3.22)
- Among respondents reporting major chronic diseases, the HR for melanoma was 2.24 (95% CI, 1.05-4.78)
- After excluding users of other treatment for ED, the association of sildenafil and melanoma remained statistically significant (HR, 2.18; 95% CI: 1.15-4.15) .
- The association between sildenafil use and melanoma after excluding the outcomes occurring in the first 2 years remained statistically significant (HR, 2.19; 95% CI: 1.18-4.07)
- The authors did not observe a significant effect of PDE5i with non-skin cancers or with other major cancers, but specific hazard ratios were not provided.

*Reviewer’s Comment: In a March 4, 2016, consultative review of this study, conducted at the request of DBRUP, the Division of Epidemiology (DEPI) in the Office of Pharmacovigilance and Epidemiology (OPE) noted that of the 142 total melanoma cases reported, 14 cases were exposed to sildenafil and 128 were not exposed to sildenafil. Since melanoma and nonmelanoma skin cancer share major risk factors, the authors concluded that sildenafil use and the apparently increased risk of melanoma, but not other skin cancers, was likely due to some other risk factor. The sensitivity analyses make the association between sildenafil and melanoma even less likely.*

*With respect to biological plausibility, OPE stated that the published literature suggests both pro- and anti-tumor effects of sildenafil in melanoma. The biological plausibility of sildenafil in increasing melanoma risk in the human population is unclear.*

*OPE was of the opinion that the study suffers from major methodological flaws, including:*

- *Recent drug exposure was evaluated as sildenafil use at baseline. Future drug exposure was not updated during the study. Any new use of sildenafil after 2000 would thus be misclassified as ‘never users.’ This could result in an underestimate of the risk of sildenafil use and melanoma. There is no information on dose or frequency of sildenafil at any time.*
- *The authors did not explicitly justify their hypothesized drug exposure risk window of the transient sildenafil exposure (hours) relative to the risk of an outcome with an assumed relatively long induction period. In their analyses, the authors assume that transient sildenafil exposure is sufficient to increase risk or that baseline self-reported usage is an accurate proxy for long-term cumulative exposure of multiple sildenafil use from 2000 to 2010. It is also not made clear that sporadic ad lib (prn)*

*sildenafil use is sufficient to stimulate the dramatic increase in melanoma cell invasion in melanoma cell lines as reported by Arozarena et. al.<sup>9</sup>*

- *The period of risk in the study requires an assumption that sildenafil exposure did not subsequently change during the ten-year follow-up study period, particularly for the initially non-exposed.*
- *Residual confounding of covariates cannot be excluded in long latency outcome analysis due to poor to moderate reproducibility of self-reported exposure measurement.*
- *14 or 142 melanoma cases in the study reported sildenafil exposure. The relatively wide 95% confidence interval (1.04 to 3.22) reflects the uncertainty in the magnitude of the hazard ratio of 1.8.*

*OPE's conclusion was that because of the major biases and assumptions in the current study, the conclusions are insufficient to recommend regulatory action at this time. Any valid study would need to consider the relationship with actual sildenafil dose and frequency.*

*OPE recommended that a future study would need to stratify on persons with and without BRAF mutation; should consider tumor stage and grade, and should evaluate the effect in men less than 65 years and in those 65 years and above. In addition, the effects of other PDE5i, such as vardenafil and tadalafil, would need to be considered, although tadalafil users may have a higher exposure to PDE5 inhibition compared to sildenafil and vardenafil due to its longer half-life.*

*Reviewer's Comment: This study did not differentiate between melanoma stages other than to state that these were all invasive cases of melanoma. While participants were asked about sildenafil use in the year 2000, there was no update on the frequency of use of sildenafil or data on the use of other PDE5 inhibitors. This abbreviated collection of data precludes a dose-response analysis. Based upon the exclusion criteria discussed above, selection bias could be present. The elimination of patients receiving other ED treatments is of concern. ED alone may be a risk factor for cancer (refer to the J Sex Med article discussion in this review). Finally, this prospective cohort was not created to study the causal association of sildenafil and melanoma. The 25,848 men studied for 10 years were a subgroup of the larger 51,529 man cohort, and the subset was used to evaluate a hypothesis that was generated after the study had started.*

*It is also notable that in their PSUR for NDA 21368 (tadalafil) April 16, 2014 to October 15, 2014, Lilly commented on results from in vitro studies suggesting that PDE5i is associated with decreased (not increased) tumorigenesis in a variety of cancers. In addition, there are no studies elucidating whether PDE5 inhibition may have an etiologic role in the development of melanoma separate from being a biomarker of invasive melanoma cell lines. Finally, sildenafil also has been shown to have anti-inflammatory effects upon melanoma cells which may play a beneficial role in melanoma therapy*

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<sup>9</sup> -Arozarena, Sanchez-Laorden, Packer, Hidalgo-Carcedo, Hayward, Viros, Sahai, Marais, 2011, Cancer cell, 19(1): 45-57.

*It is also worth noting that the European Medicines Agency (EMA), in their November 6, 2014, PRAC recommendation noted that even if some in vitro studies suggest potential mechanisms for PDE5i to promote tumor growth; their clinical relevance may be doubtful taking into account the short half-life of sildenafil. They further state that in cell lines with low expression of PDE5A (and consequently a high potential for invasion), the contribution of PDE5i is limited. While there are proposed mechanistic melanoma paths affecting proliferation or growth retardation in tissue culture, EMA questioned whether they are clinically relevant.*

**2. The 2006-2012 cohort study in Swedish men conducted by Loeb et al that investigated a possible association of PDE5i and melanoma. The results of this study were published in the June 2015 edition of JAMA (Volume 313, pages 2449-2455).**

In this study, Loeb et al reported that use of PDE5i inhibitors was associated with a modest but statistically significant increased risk of melanoma; however, the author's stated that the pattern of association (e.g., the lack of association with multiple filled prescriptions) raises questions about whether the association is causal.

*Reviewer's Comment: The reader is referred to the detailed review of this publication by the Division of Epidemiology (DEPI) in the Office of Surveillance and Epidemiology (OSE).*

This study utilized unique person identity number to study a comparison cohort of the Prostate Cancer Data Base Sweden (PCBaSe 3.0). This cancer-free comparison group consisted of 614,601 persons who had been randomly selected from the male Swedish population to match Swedish men with prostate cancer on year of birth and county of residency on a 1:5 ratio. Melanoma cases were identified from the Swedish Melanoma Registry. From this registry, information on location and stage of melanoma were then categorized by stage; stage 0 (melanoma in situ, not N<sub>1</sub> or M<sub>1</sub>), intermediate stage: stage 1 (Breslow thickness ≤ 1mm, not N<sub>1</sub> or M<sub>1</sub>) and advanced stage II through IV (Breslow thickness ≥ 1mm or N<sub>1</sub> or M<sub>1</sub>). Controls from the comparison cohort of the Prostate Cancer Data Base were then randomly selected at a ratio of 5:1 to melanoma cases using incidence density sampling, stratified on year of birth from men who were cancer-free at the date of diagnosis for the index case.

In this study, Loeb et al also studied the following:

- The association between PDEi and risk of basal cell carcinoma of the skin
- The number of prescriptions filled for PDE5i by patient and the relationship to melanoma risk.
- Separate analyses were performed to examine use of specific PDE5i (sildenafil and vardenafil, or tadalafil with its longer half-life)
- Cases were analyzed by stage
- Data on educational level, income, marital status, medical co-morbidity

The study identified 4065 men previously cancer-free with melanoma during the 2006-2012 study periods and was compared to 20325 cancer free male controls. Of the 4065 melanoma

cases, 435 had filled prescriptions for PDEi as did 1713 men of 20325 controls (8%) (Crude OR 1.31 [95% CI, 1.17-1.47]). In multivariate analysis, an increased risk of melanoma remained in men with filled PDEi prescriptions (OR, 1.21 [95% CI, 1.08-1.36]).

In multivariable analysis, the risk of melanoma was increased for men who had filled a single prescription (OR, 1.32 [95% CI, 1.10-1.59]; 4% for cases vs 3% for controls) but not for men who filled multiple prescriptions. In men whose first prescription was filled within 1 year of melanoma diagnosis the risk was also increased (OR 1.27 [95% CI, 1.09-1.48]).

There was an increased risk of melanoma among married men, those with a higher educational level, those with higher annual income and among men with higher levels of comorbidity.

PDE5i use was associated with stage 0 (1.49 [95% CI, 1.22-1.83]; 13% for cases vs 8% for controls) and stage I melanoma (OR, 1.21 [95% CI, 1.02-1.43]; 12% for cases vs 10% for controls), but not with stages II through IV melanoma (OR, 0.83 [95% CI, 0.63-1.09]; 6% for cases vs 7% for controls). Among men younger than 75 years at diagnosis, the relationship between PDE5i and melanoma was only significant for stage 0 melanoma among men with a single filled prescription.

The association with melanoma was similar for the 3 PDE5i: sildenafil (OR, 1.14 [95% CI, 0.99-1.31]), and vardenafil or tadalafil (OR, 1.16 [95% CI, 0.99-1.37]). A separate analysis was performed on 110 men who only ever used sildenafil and the 158 men who only ever used vardenafil or tadalafil. There was a statistically significant association with melanoma in men who used sildenafil only (OR, 1.27 [95% CI, 1.08-1.48]), and men who used vardenafil or tadalafil only (OR, 1.27 [95% CI, 1.09-1.48]).

There was also an association between PDE5i and basal cell carcinoma (adjusted OR, 1.19 [95% CI, 1.14-1.25]). This association was significant for all types of PDE5 inhibitors.

In the author's opinion:

- The use of PDE5i was associated with a modest but increased risk of malignant melanoma.
- The association was similar for short-acting and long-acting PDE5i and was significant for low stage but not high stage melanoma.
- The longer half-life of tadalafil did not increase the risk of melanoma.
- There was a significant association between the uses of PDE5i with basal cell carcinoma.
- The authors question whether this association of PDE5i use is causal for melanoma and basal cell cancer. Basal cell cancer served as negative control.
- A positive study feature was use of a nationwide prescription register allowing cumulative exposure.
- No association was found between sildenafil and other PDE5i with advanced stage melanoma.
- It is possible that the observed relationship of PDE5i with early stage melanoma reflects residual confounding from differences in lifestyle factors (such as leisure

travel with ensuing sunburns) and health care seeking behavior. In Sweden, PDE5i are not subsidized.

In their 27 April 2016 consultative review of this study, OSE had the following key comments:

- The Loeb study is primarily a planned hypothesis testing-exercise, whereas the Li study was intended as a hypothesis-generating study with few *prior* hypotheses.
- The Loeb study conducted analyses to evaluate consistency of estimates for sildenafil, tadalafil and vardenafil.
- Swedish national data is one of the most comprehensive sources of pharmacoepidemiologic data available.
- There is no estimate of the completeness and data quality of the Swedish Melanoma Register.
- The study has limitations which preclude establishing a causal association between PDE5i use and risk of malignant melanoma, as follows:
  - Increased risk was observed with the use of 1 PDE5 inhibitor but not with use of two or more PDE5i types
  - Failure to demonstrate dose response and dose duration relationship
  - Risk of melanoma was similar for long- and short-half life products
- There is residual confounding, particularly for life style factors that are associated with use of both PDE5i exposure and occurrence of melanoma, such as:
  - Higher socioeconomic status (more recreational sun)
  - Higher educational level
  - BMI is inversely correlated with melanoma (higher BMI acts as a proxy for less sun exposure)
  - Detection bias (affluent visit doctors more often)
- The study findings do not support the hypothesized underlying biological mechanism, as evidenced by:
  - The statistically increased risk of BCC (a negative control) which is known to be caused by sun exposure and not by the RAS/RAF/MET/ERK signaling pathway
  - No information was provided about the BRAF mutation. Arora et. al.<sup>10</sup>, suggest the signal *in vitro* between PDE5i and melanoma is present only in mutated BRAF gene.
- Computerized pharmacy dispensing records were used as a proxy measure for actual drug exposure and this is suboptimal because:
  - Exposure misclassification is possible due to intermittent use of drug
  - Out-of-pocket expense is not captured by the administrative data as lifestyle drugs are often regulated by strict quantity allowance by government-funded insurance programs
- Some subgroup analyses may have been underpowered.

In their consultative review, OSE also cited another relevant study, as follows:

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<sup>10</sup> Arora et. al., op. cit.

- Using the UK Clinical Practice Research Datalink (CPRD), researchers from McGill University, Canada (Lian Yi, et al), conducted a population-based cohort study among 142,983 men newly diagnosed with ED between January 1, 1998 and June 30, 2014 and followed until June 30, 2015<sup>11</sup>. PDE5i use was modeled as time-varying exposure, and Cox proportional hazards models were used to estimate adjusted hazards ratios. No details of covariates were provided in the abstract. During 698,479 person-years of follow-up, the investigators found 3,673 newly diagnosed non-melanoma and 440 melanoma skin cancers. Compared with non-use, the use of PDE5i was associated with a modest increased risk of non-melanoma skin cancer overall (HR=1.08, 95% CI 1.00-1.16), but there was no clear relationship in terms of number of prescriptions and pills received. In addition, the authors reported a non-significant overall increased risk of melanoma (HR=1.18, 95% CI 0.95-1.47). Furthermore, the risk was significantly increased among those who had received  $\geq 7$  prescriptions and  $\geq 25$  pills (HR=1.30, 95% CI 1.01-1.69; HR=1.34, 95% CI 1.04-1.72, respectively). These authors concluded that the use of PDE5i was associated with an increased risk of melanoma skin cancer that varied in duration-dependent fashion.
- OSE was of the opinion that the Lian et al study findings directly contradict the proposed biological mechanism for PDE5i risk of melanoma based upon the modest significantly increased risk of non-melanoma skin cancer, not melanoma skin cancer, associated with use of PDE5i. OSE stated that this study report lacked details as how the on/off time varying exposure was defined, the completeness and validity of melanoma diagnosis in CPRD data, and confounders that were adjusted in Cox regression models. Nonetheless, DEPI stated it was premature to give full assessment of the Lian et al (CPRD) study.

*Reviewer's Comment: This study was of relatively short duration (6 years). This study also lacked data and analysis relating to melanoma risk factors. This study does not demonstrate dose response or duration response.*

*Reviewer's Comment: Overall, DEPI found that due to methodological limitations of both the Loeb et al. and Li et al. studies, there was not currently sufficient epidemiologic evidence to support an association between PDE5i exposure and increased risk of malignant melanoma. DEPI recommended no regulatory action other than continued monitoring of the literature of this potential safety issue.*

### **4.3 Summary of Drug Use Data**

In the year ending February 2016, approximately 4.7 million patients received dispensed PDEi prescriptions, mostly for sildenafil or tadalafil. More than 90% of these patients were 40 years old or older, with the bulk of patients between 40 and 64 years of age (information derived from OSE Drug Utilization Review dated July 11, 2016). Of the 4.7 million patients, approximately

<sup>11</sup> Lian, Yin, Pollak, Carrier, Platt, Azoulay, 2016, Paper presented at the ISPE Mid-Year Meeting

78,000 received avanafil, approximately 2,360,000 received sildenafil, 2,450,000 received tadalafil and 361,325 received vardenafil. U.S. retail pharmacies dispensed approximately 104 million PDE5i prescriptions between March 2010 and February 2016, 49 million (47%) of which were for sildenafil and 44 million (43%) were for tadalafil.

#### **4.4 Review of Postmarketing Adverse Event Reports**

In 2015, DBRUP became aware of an increasing number of reports of melanoma in patients who had taken sildenafil and tadalafil. Most of the reports were submitted by lawyers.

In 2016, in response to a still increasing number of postmarketing AE reports of melanoma in Viagra users (still mostly from lawyers), the Division determined that the issue should be further investigated as a Tracked Safety Issue (TSI). TSI #1571 was opened.

To initiate TSI#1579, the Division of Pharmacovigilance II (DPVII) was asked to identify all postmarketing reports of melanoma in users of the PDE5 inhibitors (PDE5i) sildenafil, tadalafil, vardenafil and avanafil. On January 12, 2016, the FAERS database was searched. The time period of the search was from January 1, 1969 through December 31, 2015. The product terms were sildenafil, avanafil, tadalafil and vardenafil. 135 cases were identified. 131 of these reports were from the US and 4 were foreign. 129 of these reports were male and 6 reports did not list the patient's gender. A total of 130 cases were identified for the years 2011 to and including 2015. Of these 130 cases, 108 were submitted by attorneys, 5 were submitted by health care practitioners, 16 were submitted by consumers and 1 was reported in the literature. This section of the review provides an overview and summary analysis of these 130 cases.

*Reviewer's Comment: OSE chose the time period from 2011 through 2015 to allow sufficient market penetration for reasonable sample size for both Cialis and Viagra. In addition, since known carcinogens exhibit an additive and cumulative carcinogenic effect over time, the 2011 through 2015 time frame might allow detection of such effects.*

The following two tables summarize the number of relevant reports received for Viagra and Cialis, respectively, for years 2011 to 2015. The tables also include data on distribution or cumulative use during that time period to provide a perspective on reporting rates.

**Table 2: Summary of Postmarketing Reports of Melanoma for Viagra (NDA 20895)**

<b>Preferred Term</b>	<b>Oct 2010 to Oct 2011</b>	<b>Oct 2011 to Oct 2012</b>	<b>Oct 2012 to Oct 2013</b>	<b>Oct 2013 to Oct 2014*</b>	<b>Oct 2014 to Oct 2015</b>
Malignant Melanoma		1		5	61
Malignant Melanoma - stage IV				2	2
Melanoma - recurrent					2
Metastatic malignant Melanoma					4
Nodular Melanoma					1
<i>Estimates of US patients dispensed prescription for Viagra (in year ending.)*</i>	(b) (4) (2/2011)	(b) (4) (2/2012)	(b) (4) (2/2013)	(b) (4) (2/2014)	(b) (4) (2/2015)

Sources: Annual Reports NDA 20895; OSE Drug Utilization Review

\* Total U.S. use from March 2010 through February 2016: (b) (4)

**Table 3: Summary of Postmarketing Reports of Melanoma for Cialis (NDA 21368)**

<b>Preferred Term</b>	<b>Oct 2011</b>	<b>Oct 2012</b>	<b>Oct 2013</b>	<b>Oct 2014*</b>	<b>Oct 2015</b>
Malignant Melanoma	1	1	1	2	3
Melanoma Recurrent		1	1	1	
Metastatic malignant Melanoma					1
Choroid Melanoma	1	1	1	1	
Malignant Melanoma in situ				1	1
<i>Cumulative Use in patients world-wide</i>	$34 \times 10^6$ thru 15 Oct 2011	$39 \times 10^6$ thru 30 Sep 2012	$45 \times 10^6$ thru 30 Sep 2013	$50 \times 10^6$ thru 30 Sep 2013	$55 \times 10^6$ thru 30 Sep 2015
<i>Estimates of US patients dispensed prescription for Cialis (in year ending.)§</i>	(b) (4) (2/2011)	(b) (4) (2/2012)	(b) (4) (2/2013)	(b) (4) (2/2014)	(b) (4) (2/2015)

Sources: PSUR for NDA 21368 and OSE Drug Utilization Review

§ Total US use from March 2010 through February 2016: (b) (4)

*Reviewer's Comment: It is to be noted that the increase in reports of melanoma for Viagra began in 2014. There was no comparable increase in 2014 or beyond for Cialis. The Li et al article publication (JAMA Internal Medicine published on line April 7, 2014) coincides with the increase. The Li article deals only with sildenafil. The lack of increasing numbers of reports of melanoma in patients who took tadalafil does not support a drug class effect and supports the contention that the increase likely reflects solicited reporting.*

Of the 130 cases, 120 cases were for Viagra/sildenafil (including 1 case reporting Revatio) and 10 were for Cialis/tadalafil. Of these, 121 were male patients. The patient's gender was not specified in 9 cases. In 96 cases, the indication was erectile dysfunction, in 1 patient the indication was pulmonary arterial hypertension, and in 33 patients the indication was not stated. The youngest patient was 39 years of age and the oldest was 87 years old. In 87 of 130 cases, the patient's age was not stated. The age distribution, typical of the ages in which melanoma occurs, is shown in the table below:

**Table 4: Age Distribution for Postmarketing Reports of Melanoma in the 130-Case Cohort**

Age Band (years of age)	Number of Cases
39-48	4
49-58	8
59-68	17
69-78	13
79-88	1

*Source: Reviewer's summary of the 130 cases*

Of the 130 cases, there was information regarding calendar years exposed (as an estimate of exposure duration) in 55 cases. Table 5 provides a summary of the calendar years in which these 55 patients took PDE5i. Of note, the case reports did not provide information to estimate frequency of use. Refills were mentioned in just 20 patients. Despite the limited information, there does not appear to be any trend related to duration of treatment.

**Table 5: Calendar Years of Use in the Postmarketing Reports of Melanoma in the 130-Case Cohort**

Calendar years	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	19
Number of subjects	2	4	4	5	6	4	4	6	4	3	3	3	3	2	1	1

*\*No subjects were exposed to PDE5i for calendar years 16, 17, 18.*

*Source: Reviewer's summary of the 130 cases.*

With regard to dose strength and time from first dose to diagnosis of melanoma, the information in the case reports was sparse. As shown in Table 6, the numbers of patients with information on dosage and time from first dose to diagnosis of melanoma are small. There does not appear to be any trends related to dose.

**Table 6: Dosage Strength and Time in Months from First Dose of PDE5i until Diagnosis of Melanoma in the Postmarketing Reports of Melanoma in the 130-Case Cohort**

Months From 1 <sup>st</sup> Dose	1-12	13-24	25-36	37-48	49-60	61-72	73-84	85-96	97-108	109-120	121-132	133-144	145-156	157-168	169-180*	205-216	Total
V 50mg	1	4	1	0	2	2	1	1	1	1	2	0	0	1	0	0	17
V 75mg								1									1
V 100mg	2	2	1	3	2	0	0	1	0	0	1	0	0	1	0	1	14
Dose not stated	2	10	3	6	9	6	5	6	4	2	1	2	2	1	1		60
Total	5	16	5	9	13	8	6	9	5	3	4	2	2	3	1	1	92

V=Viagra, Upper column headings are months from first dose, Blank =no data.

\*there were no cases from weeks 181 to 204.

Source: Reviewer's summary of the 130 cases with cases with data allowing time to diagnosis analysis.

*Reviewer's Comment: In Table 6, in the 92 patients where the time of the first dose could be established, there does not appear to a dose or duration effect. This time after first dose of melanoma occurrence analysis does not suggest a causal effect.*

With regard to dosage strength, tumor stage, and time from first dose to diagnosis of melanoma, the information in the case reports was also sparse. As shown in Tables 7 and 8, the numbers of patients with information on dosage strength, tumor stage, and time from first dose to diagnosis of melanoma are small. There does not appear to be any trends related to dosage strength, tumor stage, and time to diagnosis after first dose.

**Table 7: Stage of Melanoma and Time in Months from First Dose of PDE5i until Diagnosis of Melanoma in the Postmarketing Reports of Melanoma in the 130-Case Cohort**

Months from 1 <sup>st</sup> Dose	1-12	13-24	25-36	37-48	49-60	61-72	73-84	85-96	97-108	109-120	121-132	133-144	145-156	157-168	169-180*	205-216	total
TNM Stage																	
TIS	2		1	1			1	1	1	1							8
T1		2									2		1				5
T2	1				1		1	1			1			1			6
T3		4			3	1											8
T4				1													1
M+		1		1							1						3
N+			1							1							2
Not stated	2	9	3	6	9	7	4	7	4	1	1	2	1	2	1		59
Total	5	16	5	9	13	8	6	9	5	3	5	2	2	3	1	1	93

For the cases in this table, the case mentioned Viagra (n=17), 75mg (n=1), 100 mg (n=14);

No stage mentioned in 61 cases.

*Reviewer's Comment: Table 7 does not indicate an increase in stage or in occurrence over time after first Viagra dose. This does not support a causal effect in my opinion.*

**Table 8: Tumor Stage and Dosage Strength of PDE5i in the Postmarketing Reports of Melanoma in the 130-Case Cohort**

	V 50 mg	V 75 mg	V 100 mg	Total
TIS	2	1	2	5
T1	2		1	3
T2	2		2	4
T3	1		2	3
T4			1	1
N+	1			1
M+	1			
Not stated	10	0	5	17

Source: Reviewer's summary of the 130 cases with cases with data allowing this analysis.

*Reviewer's Comment: As shown in Table 8, an analysis of tumor stage at diagnosis and dosage strength does not appear to support a causal effect.*

With regard to patients with PDE5i prescription refills, the information in the case reports was also sparse (see Table 9 below).

**Table 9: Patients with Documented PDE5i Refills in the Postmarketing Reports of Melanoma in the 130-Case Cohort**

FAERS Case ID #	Viagra Dose (mg)	Start year	Refills	First Dose to Diagnosis (months)	Calendar years in which used (unless stated)	Tumor Stage
11797349	50	2008	2	71	6	Death Jan14
11797350	100	2006	34	96	8	Not stated
11797351	100	2004	2	12	6 months	T2
11797353	100	2000	11	166	14	Death Nov13
11802186	100	2009	10	49	4 years	Not stated
11802188	50	1999	3	60	2	Not stated
11802189	50	2002	4	51	7	T2
11803393	75	2006	4	96	9	TIS
11803441	100	2000	11	165	13	T2
11803448	50	2003	2	127	10	T1
11803449	50	2013	6	19	2	T3
11806736	100	1998	7	207	11	TIS
11806738	100	2010	13	48	5	M+Jun14
11806747	50	2004	10	21	11	T1
11806870	50	2010	86	45	5	TIS
11806873	50	2004	48	81	8	Not stated
11806875	100	2007	56	59	6	T3
11806954	50	2008	12	81	8	T1
11807289	50	2003	16	103	9	TIS
11807422	50	1999	29	117	13	TIS
11807423	50	2001	30	132	11	T2

Source: Reviewer's Summary of the 130 Cases

*Reviewer's Comment: With only 21/130 patients having documentation of prescription refills, the data is insufficient to reach any conclusion relating to frequency of use, causality, or stage at presentation.*

With regard to patients with multiple tumor lesions, the information in the case reports was also sparse (see Table 10 below).

**Table 10: Patients with Multiple Melanoma Lesions (not Metastatic) in the Postmarketing Reports of Melanoma in the 130-Case Cohort**

FAERS case ID	Calendar Years Used	Patient Age	Dose	Date Primary Lesion Diagnosed	Location of Primary Lesion	Date Secondary Lesion(s) Diagnosed	Location of Secondary Lesion
10935771	2008-2012	ns	ns	2013	ear, cheek		
10935768	2009-2013	ns	100mg	2011	ns	ns*	ns
11031930	2009-ns	ns	ns	ns	head, neck		
11031938	2000-2014	ns	ns	2002	shoulder, nose, ear, forearm @same time	2002	Nose, ears, forearm
11090630	2011-2013	ns	ns	2013	scalp, neck		
11103223	2001-2012	ns	50mg	2003	nose	2012	ear
11276788	2004-2014	ns	ns	2012	scalp	2013	chin
11467912	2008-2015	ns	ns	2013	lesions back	2013 (3 mos. later)	back
11768923	2007-2015	ns	ns	2010	back	2014	chest, arm, shoulder
11806736	1998-2010	67	100mg	2015	chest, arm		

\*stated as skin cancer; ns=not stated

Source: Reviewer's Summary of 130 cases.

*Reviewer's Comment: 10/130 subjects had multiple melanoma lesions either occurring simultaneously or sequentially. There is insufficient data to document a dose effect. If PDE5i's were causal in these events, it seems that a larger number of subjects with multiple sequential lesions would have been reported.*

With regard to primary tumor lesion body location and patient age, the information in the case reports is fairly limited (see Table 11 below), but in general, the data appears to reflect the usual body locations for primary lesion of melanoma.

**Table 11: Primary Lesion Occurrence Site in the Postmarketing Reports of Melanoma in the 130-Case Cohort; Comparison Group Data Shown For Reference**

Anatomic site in German Study <sup>12</sup> (Male Comparison Group)	Percent in German Study	Median age in German Study	Number of Primary Sites in the 130-Case Cohort	Percent of Primary Sites in the 130-Case Cohort
Face	8.2	66	15	21.7
Ear			2	2.9
Scalp	5.1	64	7	10.1
Neck	2.2	57	4	5.7
Shoulder			6	8.7
Anterior trunk	16.3	55	7	10.1
Posterior trunk	39.3	55	6	8.7
Genital region	0.2	59	2	2.9
Upper extremity	12.2	58	4	5.7
Lower extremity	16.5	52	6	8.7
Multiple sites - not specified			1	1.4
Maxillary sinus			1	1.4
Buttock			1	1.4
Subungual			1	1.4
Total	96		69	

\*10 patients with multiple sites

Source: Reviewer's Summary of 130 cases with data allowing this analysis.

The distribution of sites in the table above reflects the slightly older average age of subjects in the German study (male comparison group) compared to patients using a PDE5i. In light of some subjects having multiple sites of melanoma, the number of the number of subjects with sufficient information for Table 11 is less than 69. Of note, the patient with the buttock melanoma lesion was 51 years of age and the patient with the subungual lesion was 46 years of age. Subungual melanoma comprises 0.7-3.5% of melanoma cases in the general population with peak occurrence in the 5<sup>th</sup> to 7<sup>th</sup> decades of life. It is more frequent in African Americans, Asians, and Native Americans and may account for up to one third of the melanoma cases in these population groups.<sup>13</sup> The maxillary sinus location for melanoma is unusual. The patient was 59 years of age. Mucosal melanomas of the sinonasal tract are infrequent and account for less than 1% of melanomas. Melanocytes derived from neural crest tissue are distributed throughout the upper aerodigestive tract in all races. The precise etiology of sinonasal malignant melanoma is unclear. The presence of long term melanosis in the case of oral cavity tumors is the most clearly known association. Occupational exposure to formaldehyde has also been reported as a possible risk factor.<sup>14, 15</sup>

DPV II also conducted an analysis of melanoma occurrence site in the 209 postmarketing cases reported from Viagra approval until January 20, 2016. DPV's analysis also did not reveal a disproportional incidence of melanoma at unique or unusual sites that could indicate a causality signal.

<sup>12</sup> Garbe C and Leiter U, 2009, Clinics in Dermatology 2009:27: pages 3-9.

<sup>13</sup> Levit, Kagen, et. al., Journal of the American Academy of Dermatology 2000: 42 (2) Part1, pages 269-274

<sup>14</sup> Clifton, Harrison et. al., The Journal of Laryngology and Otolaryngology, 2011: 125 pages 479-485

<sup>15</sup> Moreno, Roberts et. al., Cancer, 2010: 116(9) pages 2215-2223.

*Reviewer's Comment: The few melanomas occurring in unusual sites do not support a conclusion of PDE5i causality.*

Table 12 below shows a list of patients who had data on dose duration. Where the case report described use of a higher dose of Viagra, there is no evidence of a dose effect. It is to be noted that some subjects were diagnosed with melanoma and continued taking Viagra; therefore, in those patients, the duration of use shown in the table is longer than time to diagnosis.

**Table 12: Patients with Data on Dose Duration in the Postmarketing Reports of Melanoma in the 130-Case Cohort**

FAERS ID #	Duration of Use by Calendar Years* (If less than 1 year, in months)	Highest Dose Used	Refills	Tumor Stage at Presentation	Onset Months after 1 <sup>st</sup> dose
	0-5 years				
11797351	6 months	100mg	2	T2	12
11803449	2	50mg	6	T3	19
11806738	5	100mg	13	T4	48
11806748	4	100mg	ns	TIS	12
11806757	4	ns	ns	TIS	36
11807287	3	100mg	ns	T3	18
11829172	4	ns	ns	fatal	44
10935771	5	ns	ns	T3	54
10975676	2	ns	ns	fatal	22
11701722	4	ns	ns	T3	54
11738113	5	50mg	ns	N+	36
11786775	3	ns	ns	M+	24
	6-10 years				
11802819	7	50mg	4	T2	51
11802226	6	ns	ns	T1	18
11803393	9	75mg	4	TIS	96
11806739	9	ns	ns	TIS	78
11806875	6	100mg	56	T3	59
11806954	9	100mg	8	T1	81
11807289	9	100mg	16	TIS	103
10530385	10	50mg	ns	T4	120
11038223	10	ns	ns	T3	24
11058229	7	ns	ns	T2	78
	10-15 years				
11803439	15	ns	ns	T2	169
11803448	12	50mg	2	T1	127
11803441	13	100mg	11	T2	165
11806870	15	100mg	86	TIS	45
11807422	13	100mg	29	TIS	117
11760613	12	ns	ns	+N	119

\*patients had to have Viagra start date, stop date, tumor stage, and onset date after first dose  
n.s. = not stated

*Reviewer's Comment: I do not discern a relationship between duration of use or dose and the stage of melanoma at initial diagnosis.*

Among the 130 postmarketing reports, there were 11 deaths due to melanoma. Table 13 below provides an overview of those 11 death cases.

**Table13: Deaths Due to Melanoma in the Postmarketing Reports of Melanoma in the 130-Case Cohort**

	PDE5i Starting Dose (in mg)	PDE5i Start Year	PDE5i End Year	Number of Refills	Patient Age	Number of Calendar Years Used	Number of Years From PDE5i Start to Diagnosis	Stage At Diagnosis	Number of Years From PDE5i Start to Death
(b) (6)	Viagra ns	2002	2011		39	10	11	death	11
	Viagra ns	2000	ns		ns	9		death	10
	Viagra ns	2002	ns			ns	4	ns	ns
	viagra ns	2004	ns		ns	ns	6	death	6
	Viagra ns	2011	2012		65	2	2	death	2
	Viagra ns	2000	2007		ns	8	9	death	9
	Viagra ns	1998	ns			ns	12	Stage IV	15
	Cialis 20 mg	2009	2013		ns	5	5	ns	5
	Viagra 50mg	2008	2013	2	61	6	6	death	6
	Viagra ns	2009	2012		ns	4	4	mets	4
	sildenafil	ns	ns		73	ns	May predate	mets	ns

*ns=not stated; Stage at time of diagnosis = verbatim from report; Patient age = as stated in report, time periods stated in years = any part of a calendar year counted as a full year. Source: Reviewer's Summary of 130 cases.*

The following brief narratives for these 11 death cases are based on information provided in the case reports:

**Case ID:** (b) (6): Manufacturer received report 22 December 2014. This 39 year old US male was placed on Viagra for erectile dysfunction which he took at a not stated dosage and frequency from 2002 until 2011. The relevant medical history, concomitant medications, past drug history and laboratory history are unknown. There is no analysis of patient melanoma risk factors. At an unknown date, he was diagnosed with melanoma, stage not included in report. The treatment he received is unknown. On (b) (6), he died due to melanoma. The report is submitted by an attorney and contains no pathology, autopsy or other medical reports or references to them.

**Case ID:** (b) (6): Manufacturer received report 11 February 2015. This US male of unknown age was placed on Viagra for erectile dysfunction at an unstated dose and frequency. The patient ingested Viagra from August 2000 to an unknown date. The relevant medical history, concomitant medications, past drug history and laboratory history are unknown. There is no analysis of patient melanoma risk factors. At an unknown date, he was diagnosed with melanoma, stage not included in report. The treatment he received is unknown. In (b) (6), he died due to melanoma. The report is submitted by an attorney and contains no pathology, autopsy or other medical reports or references to them.

**Case ID:** (b) (6): Manufacturer received report 11 February 2015. This US male of unknown age was placed on Viagra for erectile dysfunction at an unstated dose and frequency. The patient ingested Viagra from January 2002 until an unknown date for erectile dysfunction. The relevant medical history, concomitant medications, past drug history and laboratory history are unknown. There is no analysis of patient melanoma risk factors. At an unknown date in (b) (6), he was diagnosed with melanoma, stage not included in report. The treatment he received is unknown. In (b) (6), he died due to melanoma. The report is submitted by an attorney and contains no pathology, autopsy or other medical reports or references to them.

**Case ID:** (b) (6): Manufacturer received report 11 February 2015. This US male of unknown age was placed on Viagra for erectile dysfunction at an unstated dose and frequency. The patient ingested Viagra from February 2004 until an unknown date for erectile dysfunction. The relevant medical history, concomitant medications, past drug history and laboratory history are unknown. There is no analysis of patient melanoma risk factors. At an unknown date in (b) (6), he was diagnosed with melanoma, stage not included in report. The treatment he received is unknown. In (b) (6), he died due to melanoma. The report is submitted by an attorney and contains no pathology, autopsy or other medical reports or references to them.

**Case ID:** (b) (6): Manufacturer received report 26 March 2015. This 65 year old US male was placed on Viagra for erectile dysfunction at an unstated dose and frequency. The patient ingested Viagra starting in 2011 and ending September 2012. The relevant medical history, concomitant medications, past drug history and laboratory history are unknown. There is no analysis of patient melanoma risk factors. On (b) (6), the patient died due Stage IV melanoma. Relevant lab data was not in report. It was reported that an autopsy was performed. At autopsy it was revealed that the patient was posthumously diagnosed with Stage IV melanoma in his lungs. This is an attorney submitted report.

**Case ID:** (b) (6): Manufacturer received report 7 April 2015. This US male of unstated age was prescribed and ingested Viagra at an unknown dose and frequency from 2000 until at least 2007. The relevant medical history, concomitant medications, past drug history and laboratory history are unknown. There is no analysis of patient melanoma risk factors. On (b) (6), he died with cause of death listed on death certificate reported as pulmonary embolus due to or a consequence of metastatic mucosal melanoma. The treatment he received was not stated. It is not known if an autopsy was performed. This is an attorney submitted report.

**Case ID:** (b) (6): Manufacturer received report on 20 April 2015. This 62 year old US male was prescribed and ingested Viagra at an unknown dose and frequency from 1998 to an

unknown date for erectile dysfunction. The relevant medical history, concomitant medications, past drug history and laboratory history are unknown. There is no analysis of patient melanoma risk factors. He was diagnosed with “at least IV” melanoma and metastatic melanoma on (b) (6). The treatment received is unknown. He died on (b) (6) due to “at least IV” melanoma and metastatic melanoma according to the report. The report is submitted by an attorney and contains no pathology, autopsy or other medical reports or references to them.

**Case ID:** (b) (6): Manufacturer received report 12 August 2015. This US male of unstated age was prescribed and ingested Cialis 20 mg at an unknown frequency for erectile dysfunction between December 2009 and February 2013. The relevant medical history, concomitant medications, past drug history and laboratory history are unknown. There is no analysis of patient melanoma risk factors. On (b) (6), patient underwent melanoma excision of chest. Pathology stage is not in report. On (b) (6), noted multiple nodules surrounding the chest incision extending to the left axilla. A PET scan conducted on (b) (6) showed progression of the melanoma to left chest wall, bones, liver, pancreas and lymphatic system. The treatment he received is not stated. On (b) (6), the patient died from Stage IV metastatic melanoma according to the report. It is unknown if an autopsy was performed. This was an attorney submitted report.

**Case ID:** (b) (6): Manufacturer received report 30 November 2015. This 61 year old US male was prescribed and ingested 50 Viagra starting 30 July 2008 and ending in 2013 for erectile dysfunction. The patient refilled the prescription twice but actual frequency of use is not stated. The relevant medical history included coronary artery disease, pelvic crush injury and myocardial infarction at an unknown date. The patient used tobacco and alcohol at unknown dates. The family history includes diabetes, coronary artery disease, stroke and cancer. There is no detail of concomitant or past drug usage. There is no analysis of melanoma risk factors. The patient was diagnosed with melanoma on (b) (6). The treatment received was unknown. The patient died (b) (6) with cause of death reported as metastatic melanoma and bacterial pneumonia. It was reported no autopsy was performed. The report is submitted by an attorney and contains no pathology or other medical reports or references to them.

**Case ID:** (b) (6): Manufacturer received report 11 December 2015. This US male was prescribed and ingested Viagra at an unknown dose and frequency (“occasionally”) between February 2009 and 2012 for erectile dysfunction. The relevant medical history, concomitant medications, past drug history and laboratory history are unknown. There is no analysis of patient melanoma risk factors. In (b) (6), he was diagnosed with melanoma and on (b) (6), computed tomography of the head revealed multiple brain lesions compatible with metastatic melanoma. At an unknown date, the patient underwent whole brain radiation. The patient died (b) (6). It is unknown whether an autopsy was performed. The report is submitted by an attorney and contains no pathology or other medical reports or references to them.

**Case ID (Medwatch):** (b) (6): FDA received report May 17 2010. This report, while counted as one of the 130 reports in the cohort, was received in 2010. This report was received from a health care professional. This 73 year old US male was on sildenafil and bosentan for pulmonary hypertension. PAH was subsequent to a pneumonectomy for metastases from a basal cell

carcinoma of concha (? nasal turbinate or ear). The duration and frequency of sildenafil is not stated. The patient died (b) (6) from either PAH or metastatic melanoma. An autopsy was not performed. Warfarin was a concomitant medication. Medical or other history, laboratory, or analysis of melanoma risk factors is not provided. Reviewer's comment for (b) (6): *If the pneumonectomy was performed for metastatic melanoma as opposed to metastatic basal cell carcinoma, which is rare at sites not exposed to sunlight and metastasizes infrequently, then the resultant PAH requiring sildenafil occurred after the original melanoma diagnosis which confounds an assessment of causality to sildenafil.*

*Reviewer's Comment on Death Narratives: In their totality, the deaths lack data to document how much PDE5i was taken prior to melanoma diagnosis. While one report does document drug refills, the number of doses in each refill is not included in the report. While some reports document the duration of exposure (? from first dose), there is no indication in most reports of regular drug use during the reported duration of exposure. The indication for use in all but one patient is treatment of erectile dysfunction (ED). These reports do little to further the consideration of causality of melanoma from PDE5i use.*

*Reviewer's Overall Comments on the 130 Postmarketing Cases: In summary, for the 130 cases, most reports do not contain medical history or confounding conditions such as sun exposure, complexion, etc. There is no working definition to make the determination of a drug event relative to melanoma occurrence other than the date of melanoma diagnosis. Data is inadequate to inform a dose and time response analysis. In many reports, the time of the melanoma event is remote from the time of reporting, representing another potential confounding factor. In most cases, there is scant information to define the tumor including lack of tumor stage, grade and pathology of the excised lesion. Treatment outcome is also not well described in the majority of cases.*

*These 130 cases are FAERS reported cases. The FAERS system is used to evaluate rare adverse events associated with drugs that were not detected during drug trials. Events with a long lag time between drug use and event occurrence may be confounded by other factors. One factor apparent in these 130 cases appears to be solicited reporting. Solicited reporting may not be reflective of a true drug signal. The majority of cases do not have enough information about risk factors, duration of therapy, patient history, concomitant medications to make a correlation between drug and event. The populations of patients who receive PDE5i are generally older men who have erectile dysfunction and may already be at higher risk for melanoma independent of PDE5i use.*

*The very small number of melanoma cases with Cialis argues against a true melanoma signal for an association of PDE5i exposure and melanoma. There is no data presented to suggest an effect unique to sildenafil. The previously cited Swedish cohort study in which the risk of melanoma was similar for the 3 PDE5i (sildenafil, vardenafil and tadalafil [which is longer-acting]) argues against a unique sildenafil effect. In the same study, there was an association between PDE5i and basal cell carcinoma (adjusted OR, 1.19 [95% CI, 1.14-1.25]). This association was significant for all types of PDE5i. This*

*suggests to me that a variable may be present that is unrelated to any specific PDE5i drug or PDE5i drug class.*

#### **4.5 Review of Responses by PDE5i Sponsors to FDA Information Requests**

On June 15, 2016, an information request was sent to Pfizer, Lilly, Bayer and Vivus; the current Sponsors of US approved PDE5i drugs. The following information was requested:

Using the cases identified, provide results from the following requested analyses:

1. Compare melanoma incidence rates between drug and placebo, as well as between drug and active comparator, when available. Provide 95% confidence intervals and relative risk assessments.
2. Provide an assessment of melanoma incidence rates by dose, duration, and length of time from sildenafil citrate (*or "X" drug*) exposure to AE report.
3. Compare melanoma incidence rates between daily use and ad lib (prn) use of sildenafil citrate (*or "X" drug*).
4. In studies with no control arm, compare melanoma incidence rates to demographically-matched SEER melanoma incidence rates.
5. Identify cases in which more than one PDE5i was used by the same subject. Perform analyses with these subjects included and excluded.
6. Identify cases in which baseline risk factors for melanoma were reported. Perform analyses with these subjects included and excluded.
7. Perform analyses 1 - 6 for the incidence of basal cell carcinoma identified as AEs in clinical trials of sildenafil citrate (*or "X" drug*).

In addition, provide an overall evaluation of the data relative to the risk of melanoma in association with use of sildenafil citrate (*or "X" drug*).

The following subsections provide a description of each Sponsor's response to the FDA's IR. Each part of the Sponsor's response to the IR is outlined, followed an overall evaluation of each Sponsor's overall response, including a statement on the incidence of melanoma and basal cell cancer in clinical trials with respect to each Sponsor's individual drug product.

##### **4.5.1 Vivus: Avanafil**

Vivus, the Sponsor for Stendra (avanafil), responded to the IR on July 13, 2016.

1. Vivus identified one case of melanoma in their drug development program

2. The incidence rates of melanoma in avanafil clinical trials were determined in two ways: first with data limited to the 712 subjects treated with avanafil in the open-label extension study (TA-314), and second with data including all phase 2/3/4 clinical studies during which 1,754 subjects were treated with avanafil.

**Table 14: Incidence of Melanoma in the Avanafil Drug Development Program**

<b>Incidence</b>	<b>Study TA-314 Only N=712</b>	<b>Integrated Program N=1754</b>
Number (%)	1 (0.14)	1 (0.06)
95% CI	0.02-0.79	0.01-0.37

*Source: Table 1 of Sponsor's submission Module 1.11.3*

In the one event of melanoma reported, the subject used 25 doses of avanafil over a period of 145 days prior to the diagnosis of melanoma. During the subject's study participation, he used an additional 42 doses after the melanoma diagnosis. Prior to the melanoma event, the subject titrated up from 100 mg dose to the 200 mg dose of avanafil, but 20 of the 25 doses taken prior to the event were at the 100 mg dose level, and only 5 were at the 200 mg dose level.

3. Daily use of avanafil was evaluated in one study (TA-401). In this study, no events of melanoma were reported.
4. The study in which melanoma occurred had no control arm. Calculating incidence rates based just on one study and ignoring all other studies could result in appropriately increased incidence rates. To provide a relevant result, the Sponsor made 3 assumptions. The first was that the SEER data used for comparison would be data that applies to white males. Second, being unable to calculate precise patient-year experience in the avanafil drug development program, the Sponsor proposed to estimate this value based upon the duration of the individual clinical trials. Third, since there were two trials with treatment durations of 1 year (with open label follow-on), one trial with a treatment duration of 6 months, two trials with a treatment duration of 3 months and one trial with a duration of 2 months, the Sponsor used all 1754 subjects treated with avanafil in these trials. These subjects may have come in part from placebo-controlled studies. The Sponsor made comparisons to SEER data where treatment duration is estimated at 4, 5, and 6 months. As shown in Table 15 below, none of the confidence intervals exclude the value of 1. The Sponsor concluded that the results do not indicate a significant increase vs the SEER rate.

**Table 15: Incidence Rates of Melanoma in Avanafil Drug Development Program**

	<b>SEER Data</b>	<b>Avanafil (by Estimated Average Exposure)</b>		
		<b>4 months</b>	<b>5 months</b>	<b>6 months</b>
<b>Patient Years</b>	100,000	585	730	877
<b>Melanoma cases</b>	33.5	1	1	1
<b>Incidence rate</b>	0.34	0.171	0.137	0.114
<b>Relative Risk vs SEER (95% CI)</b>		5.10 (0.70-37.13)	4.09 (0.56-29.85)	3.40 (0.46-24.85)

*Source: Table 2 of Sponsor's submission Module 1.11.3*

5. The single patient who experienced a melanoma during the clinical trials also had prior exposure to sildenafil and tadalafil. There were no subjects with melanoma exposed to avanafil only.
6. With only one melanoma patient in the clinical program, identification of risk factors was not applicable.
7. Across the avanafil development program, basal cell carcinoma was reported by 1 placebo subject, one avanafil 100 mg subject, and one avanafil 200 mg subject. The incidence rates were calculated using data from all phase 2/3/4 clinical trials.

**Table 16: Incidence of Basal Cell Carcinoma in Avanafil Drug Development Program**

	<b>Placebo N=591</b>	<b>Avanafil 100mg N=594</b>	<b>Avanafil 200 mg N=596</b>
Number (%)	1 (0.169)	1 (0.168)	1 (0.168)
Relative Risk vs Placebo (95% CI)		0.99 (0.006 to 18.87)	0.99 (0.06-15.81)

*Source: Table 3 of Sponsor's submission Module 1.11.3*

In the Sponsor's overall evaluation, because of the scarcity of reports of melanoma, the data generated from this clinical trial program can neither confirm nor rule out a signal for an increased melanoma risk. Data from this clinical trial is further compromised by the fact approximately 70 % of the subjects treated were exposed to either sildenafil or tadalafil prior to their enrollment in avanafil clinical trials.

#### **4.5.2 Pfizer: Viagra**

Pfizer, Sponsor for sildenafil citrate, responded to the IR on July 15, 2016. The Sponsor stated that the Viagra Global Repository (VGR) contains 136 Phase 2-4 clinical studies, including randomized, placebo-controlled, double-blind, studies as well as non-placebo-controlled, parent and extension studies. The VGR includes 23,182 male subjects who took at least one dose of sildenafil and 7,498 subjects who took at least one dose of placebo during clinical trials. The dose of sildenafil in the VGR ranged from 5 mg to 200 mg, with the majority of the studies investigating 25 mg, 50 mg and 100 mg sildenafil, which are the licensed doses for Viagra in the US for ED. In nearly all of the studies, sildenafil doses could be taken as needed (PRN), but not more than once daily. The cumulative exposure to sildenafil across all the VGR is over 12,965 person-years. Most of the 136 studies were flexible-dose studies and the majority was Phase 3 or Phase 4 studies.

1. In the VGR, there were 74 double-blind placebo-controlled ED studies (74 DBPC Dataset). The double-blind (DB) phase of most of the studies included in the 74 DBPC Dataset was generally 12 weeks in duration, although the duration of some of the pivotal studies had a 6 month DB phase. Subjects in the 74 DBPC dataset were allocated to sildenafil treatment in a dose range of 5 mg to 200 mg, although the majority of the studies investigated 25 mg, 50 mg and 100 mg sildenafil.

There were an additional 5 DBPC studies within the VGR; however, they were not included as part of the 74 DBPC because of the following reasons: they investigated drug in subjects in either different populations (subjects with spinal cord injury), in subjects with no ED, or the study design included a single blind phase prior to a DB randomized phase.

In the double-blind (DB) placebo controlled (PC) dataset, there were 61 DB, PC, parallel studies and 13 DB, PC, crossover studies. In the 61 DB, PC, parallel studies, there were no preferred terms (PTs) reported as melanoma for subjects receiving treatment with Viagra and a single case reporting a PT of Malignant melanoma in a subject receiving placebo. One case of melanoma was identified from Pfizer's post-marketing safety database in a subject who received sildenafil (50 mg PRN) in a Viagra clinical study in which he had previously participated. This subject was not included in the 136-study VGR, because the adverse event occurred approximately 7 months after last dose of study drug. The total exposure to treatment was slightly higher in the Viagra treatment group compared with placebo (2000 and 1361 person-years, respectively) for the 61 DB, PC, parallel Dataset. Since there were no melanoma-related events reported in the Viagra-treated subjects, the calculated incidence rate for Viagra was zero. The incidence rate per 100,000 person-years for the placebo treated subjects from the 61 DB, PC, parallel Dataset was 64.7 (95% confidence interval [CI]: 0.000, 191.5).

**Table 17: Incidence of Melanoma in 61 DB, PC, Parallel Group Viagra Clinical Studies**

	Number of Subjects With Events	Number of Subjects in Treatment Group	Total Treatment Exposure (Person-years)	Weighted Incidence Rate per 100,000 Person-years	95% CI of Incidence Rate
<b>Viagra</b>	0	8775	2000	0.0	NA
<b>Placebo</b>	1	6457	1361	64.7	0.0, 191.5

Source: Table 3 of Sponsor's IR Response, page 15.

*Reviewer's Comment: This large number of subjects in DB, PC studies does not suggest a melanoma growth promoter effect.*

In the 13 DB, PC, crossover studies, there were no cases reporting melanoma events. These studies included 795 Viagra patients and 780 placebo patients.

Among the 136 VGR studies, there were three OL and one DB, PC trials investigating sildenafil use compared with an active comparator, including tadalafil, apomorphine hydrochloride, phentolamine mesylate and isosorbide mononitrate. There were no melanoma-related events reported in any of treatment arms in these studies; therefore, the incidence rate is zero for both Viagra and the active comparators.

There were no melanoma events reported in the 14 Revatio completed Phase 2-4 adult and pediatric studies. A total of 893 subjects were treated with sildenafil and 250 subjects were treated with placebo in the 9 adult studies; and 281 subjects were treated with sildenafil and 65 subjects were treated with placebo in the 5 pediatric studies. The

cumulative length of exposure to sildenafil was 1,652.9 person-years across all adult studies, and 998.1 person-years across all pediatric studies.

*Reviewer's Comment: These results for the above clinical studies do not indicate an increased risk of melanoma –related events with sildenafil as compared to placebo or to active comparator in the sildenafil clinical development program.*

2. The dose of sildenafil in the 136 VGR studies ranged from 5 mg to 200 mg, with the majority of the studies investigating 25 mg, 50 mg and 100 mg sildenafil. The cumulative length of exposure to sildenafil across all studies is over 12,965 years. All 136 VGR clinical studies have been used to assess melanoma incidence rates by dose, duration, and length of time from sildenafil exposure to AE report.

From the 74 DB, PC Dataset, there was 1 melanoma-related event reported in the placebo treated group, which occurred within a parallel study as discussed in answer 1.

The incidence rate for the OL (open label) Dataset was defined as the number of sildenafil-treated subjects with at least one event during the OL segment per 100,000 person-years (subject exposure to treatment). From the OL Dataset, there were 6 subjects reporting melanoma-related events in the sildenafil treated group. One subject was not included in the incidence rate calculation, because the melanoma-related event was not a TEAE in that the melanoma diagnosis was 16 days after the last dose of study drug. Of the 5 subjects with TEAE, 1 subject was in the 25 mg dose, 3 subjects in the 50 mg group and 1 subject in the 100 mg group. The range of duration of sildenafil exposure to the TEAE onset date for the 5 subjects was 35 to 907 days. The ages of all 5 patients reporting melanoma were: 69, 66, 71, 45, and 71 years of age. The average age was 64.4 years. The incidence rate of melanoma-related TEAEs per 100,000 person-years for the sildenafil-treated subjects from the OL Dataset was 37.2 (95% CI: 15.5 – 89.38). The SEER database incidence rate for patients 60-64 years of age is 66.2 per 100,000 patient years.<sup>16</sup>

The incidence rates between daily use and prn use of sildenafil could not be calculated by Sponsor for the 136 VGR dataset. Because of lack of cases reporting melanoma-related TEAEs in the 74 DB, PC dataset and small number of cases in the OL data set, further calculations split by dose, duration and length of time from sildenafil exposure were not performed.

There were no cases reporting melanoma related events from sildenafil-treated patients from the 14 Revatio completed Phase 2-4 adult and pediatric studies.

Sponsor concludes that the results of this assessment indicate no evidence of an increased risk of melanoma-related events with either sildenafil, at doses of 25, 50 and 100 mg or with Revatio (daily use of sildenafil for the treatment of PAH: adult dose 5-20 mg tid) in sildenafil clinical programs.

<sup>16</sup> SEER incidence rates for the entire SEER database and in patients <65 years and 65+ years age adjusted to the 2000 US standard population; Table 6 of Sponsor's submission, page 23.

*Reviewer's Comment: Protocol-related adverse event reporting focuses on acute events that occur either during the protocol or within a short time thereafter. This analysis will not be able to consider melanomas that occur sometime after PDE5i exposure. Nonetheless, theoretically, this analysis could possibly detect a tumor growth promoter effect, and there is no suggestion of that so far.*

3. In the 74 DB, PC dataset, there were 6 DB, PC studies that investigated the daily use of sildenafil. From these 6 DB, PC, daily use studies, there were no cases reporting melanoma-related events. From the OL dataset, there were no open-label studies with daily-use regimen. Therefore, the incidence rates between daily use and prn use of sildenafil could not be calculated for the 136 VGR dataset. There no cases reporting melanoma-related events in patients receiving Revatio.

Sponsor concludes that the results of this assessment do not indicate an increase in risk for melanoma-related events with the use of sildenafil or the daily use of sildenafil for the treatment of PAH.

4. Data retrieved from the SEER database, indicate that in a male population the melanoma incidence rate is higher in subjects over 65 years of age, compared with those below 65 years. With further stratification by 5 year age intervals, the age-dependent increase in incidence rate appears more pronounced in individuals 60 years and older.

The ages of all 5 patients reporting melanoma in the Viagra OL studies were: 69, 66, 71, 45, and 71 years of age. The average age was 64.4 years. The incidence rate of melanoma-related TEAEs per 100,000 person-years for the sildenafil-treated subjects from the OL Dataset was 37.2 (95% CI: 15.5 – 89.38). The SEER database incidence rate for patients 60-64 years of age is 66.2 per 100,000 patient years.<sup>17</sup>

This assessment does not indicate an increase of melanoma treatment related events with the use of sildenafil.

5. There were no clinical studies within the 136 VGR Database in which more than one PDE5i was used by the same subject; therefore, no analyses could be performed including and excluding such subjects based upon PDE5i use as a concomitant medication or comparator use.

In the 14 Revatio completed Phase 2-4 adult and pediatric studies, no other PDE5i were used, except for a single subject participating in a pediatric study who was prescribed tadalafil on the last day of study treatment. There were no melanoma-related events reported from the Revatio clinical study dataset and therefore additional analyses could not be performed.

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<sup>17</sup> SEER incidence rates for the entire SEER database and in patients <65 years and 65+years age adjusted to the 2000 US standard population; Table 6 of Sponsor's submission, page 23.

6. Out of the 5 cases who reported melanoma-related TEAEs from the sildenafil OL dataset, there were 2 subjects who had baseline risk factors based upon review of their medical history. One subject, (b) (6), had a documented history of malignant melanoma with no recurrent disease at the time of study entry. During study he was considered to have a relapse of his known past melanoma and eventually died from substantial metastasis of his malignant melanoma. A second subject while taking sildenafil from August 21, 1998 until November 10, 1998, on October 1, 1998, underwent excision for a lesion behind the ear. A surgery report indicated that a biopsy was done on (b) (6), which revealed a pre-existing left auricular tumor which had existed for 4-5 years and appeared to be a malignant melanoma.

There were no cases reporting melanoma-related events from the Revatio clinical dataset.

7. Basal cell carcinoma has no causal mechanistic relationship to PDE5i use. The incidence of basal cell carcinoma (BCC) has been used as a negative control in 2 melanoma epidemiologic studies. It is expected that there should be no increase of BCE in PDE5i exposed patients as compared to non -exposed to PDE5i subjects. If, therefore, an association is found between basal cell carcinoma and PDE5i use, this association may reflect confounding lifestyle factors and other factors associated with PDE5i use and melanoma occurrence and not to PDE5i use.

Analysis 1: A search of the 61 DB, PC parallel studies identified 9 subjects with the PT Basal cell carcinoma in the sildenafil-treated group and 4 subjects in the placebo group. Incidence rate for the sildenafil and placebo treated subjects per 100,000 Person-Years were 428.1 (95% CI: 133.1, 723.1) and 277.8 (95% CI: 4.7, 551.0). The relative risk was 1.54 (95% CI: 0.43, 5.46). Due to the small numbers of basal cell carcinoma cases in each treatment arms the 95% CIs for the incidence rates are quite wide. The 95% CI of the RR crosses 1.0 indicating no statistically greater risk is observed in the Viagra group.

Among the 136 VGR studies, there were three OL and one DB, PC trials investigating sildenafil use compared with active comparator, including tadalafil, apomorphine hydrochloride, phentolamine mesylate and isosorbide mononitrate. There were no cases reporting the PT Basal cell carcinoma in any of treatment arms in the studies with active comparator; therefore, the incidence rate is zero for both sildenafil and active comparator and the relative risk could not be calculated.

For Revatio, no cases of basal cell carcinoma were reported from any placebo-controlled studies. There were 3 subjects with basal cell carcinoma reported in the 2 adult long-term extension studies (A1481142 and A1481153), in which sildenafil was the only study treatment. Therefore relative risk of Revatio versus placebo could not be calculated for the incidence of basal cell carcinoma.

Analysis 2: Incidence rate for the sildenafil and placebo treated subjects per 100,000 Person-Years were 428.1 (95% CI: 133.1, 723.1) and 277.8 (95% CI: 4.7, 551.0), respectively. The relative risk was 1.54 (95% CI: 0.43, 5.46). This CI includes 1.0. The incidence rate for the OL Dataset is 141.7 (95% CI: 90.4 – 222.1) per 100,000 person-years, which was lower than the incidence rate observed in either the placebo group or the

sildenafil group in the DB, PC studies<sup>11</sup>. The incidence rate has not been further calculated split by dose, duration and length of time from sildenafil exposure to AE report. The Sponsor's reasons for not doing the calculations are complexity of study design and variability in PRN dosing.

The Sponsor provided a summary table of basal cell carcinoma cases by dose, duration and length of sildenafil exposure.

*Reviewer's Comment: Without knowing the frequency of exposure for each subject, this data is not useful for estimating risk by dose, duration and length of exposure. The complexity of the study designs and variability in dosing, in my opinion, make these analyses confounded if done. The relative risk noted in Analysis 1 is the most useful parameter thus far.*

Analysis 3: The comparison of incidence rates of basal cell carcinoma by treatment groups were calculated from the 3, daily-dose, parallel studies and 58 PRN parallel studies from the 74 DB, PC Dataset studies (61 DB, PC parallel studies). A search of the 3 daily-dose, parallel studies identified 3 subjects with the PT Basal cell carcinoma in the sildenafil-treated group (N=526) and 0 subjects in the placebo group (N=317). The incidence rate for the sildenafil treated subjects per 100,000 person-years was 2630. Since there were no cases reported in the placebo-treated subjects, the incidence rate for placebo is zero.

A search of the 58 PRN parallel studies identified 6 subjects in the sildenafil treated group (N=8249) and 4 subjects in the placebo treated group (N=6140). The incidence rates for sildenafil and placebo treated groups per 100,000 Person-years were 294.5 and 294.7, respectively. The basal cell incidence was higher in prn treated patients than it was in once daily treated patients.

*Reviewer's Comment: The reason for the discrepancy in incidence of basal cell carcinoma between daily use and PRN use is unknown, but the numbers of cases are small. Later in this review, we note that the incidence of basal cell carcinoma with daily dosing of tadalafil is slightly higher than the incidence of prn dosing. Again, this discrepancy involves small numbers and does not appear reproducible for other PDE5i's.*

Analysis 4: Reporting of basal cell carcinoma cases to cancer registries is not required in the US, and thus, these cases are not captured within the SEER database.

Analysis 5: There are no clinical studies within the VGR in which more than one PDE5i was used by the same subject.

Analysis 6: From the 136 study VGR Database, there were 28 subjects who reported the PT Basal cell carcinoma. Of these, a total of 11 subjects were identified with baseline risk factors for basal cell carcinoma based upon a review of the available medical history and those risk factors included: past or present history of malignant melanoma, solar keratosis, basal cell carcinoma, skin cancer, tobacco abuse, and nicotine dependence. One subject was placebo treated and 10 were sildenafil treated. Five subjects were from the

74 DB, PC Dataset and 6 were from the OL Dataset. These subjects have been excluded from the analysis. The Sponsor has calculated the RR for basal cell carcinoma in sildenafil treated patients compared with placebo as RR=1.07 (95% CI: 0.23-5.09).

**Table 18: Incidence Rates and 95% CI of Basal Cell Carcinoma by Treatment Group – in the 61 DB, PC Parallel Studies of Viagra**

Treatment Group	Number of Subjects with Events	Number of Subjects in Treatment Group	Total Exposure to Treatment (in Person-Years)	Weighted Incidence Rate per 100,000 Person-Years	95% CI of Incidence Rate
Viagra	5	8771	1998	226.3	[15.1, 437.5]
Placebo	3	6456	1361	211.1	[0.0, 451.0]

Source: Table 13 of Sponsor's IR Response, page 40

**Table 19: Incidence Rate of Basal Cell Carcinoma in the OL Dataset of Viagra**

Number of Subjects with Events	Total Number of Patients Treated	Total Exposure to Treatment (in Person-Years)	Incidence Rate per 100,000 Person-Years	95% CI of Incidence Rate
13	19297	13404	97.0	[56.3, 167.0]

Source: Table 14 of Sponsor's IR Response, page 40

The results of the overall analyses indicate that there are a very small number of cases in the VGR reporting melanoma-related TEAEs in sildenafil treated subjects (N=5). RR could be calculated for studies with zero events in the Viagra group and non-zero events in the placebo group but not for studies with zero events in the placebo arm. These facts limit the ability to calculate and interpret the incidence rates and RR. The Sponsor concludes a formal evaluation of potential association with dose, duration or length of treatment with Viagra would not have been meaningful. No trend or pattern was apparent. Daily dose assessment did not identify any additional melanoma events. The melanoma incidence rates for the Viagra Open Label (No Control) Dataset were in general alignment with SEER incidence rates. The relative risk for basal cell carcinoma in association with Viagra use was 1.07 (95% CI: 0.23-5.09).

Sponsor concludes that these analysis reflect no increase in risk of melanoma-related events with use of sildenafil, including both PRN therapy for ED and daily use therapy for PAH.

*Reviewer's Comment: The case number for melanoma was small. There is no indication that sildenafil is a melanoma growth promoter.*

#### 4.5.2 Bayer: Vardenafil

On July 29, 2016, Bayer responded to the FDA IR. The Bayer response pertains to both Levitra (NDA 21400) and Staxyn (NDA 200179). Both these products contain vardenafil as the active ingredient. The IR response is the cumulative experience for both products. The Bayer analyses are based on the following datasets:

- Bayer's Global Integrated Analysis Database (GIAD) which includes clinical studies from Phase II B through Phase IV for vardenafil, and

- The Safety Analysis Set (SAF).

Bayer conducted analyses using 4 data pools, as follows:

- Pool 1: Comprising 40 placebo-controlled studies (N=5,706 placebo, N=9,359 vardenafil)
- Pool 2: Comprising 9 active-controlled studies (i.e., 7 sildenafil-controlled studies: N=1,694 sildenafil, N=1,918 vardenafil; and 2 tadalafil-controlled studies: N=666 tadalafil, N=680 vardenafil)  
In this pool, in crossover studies, subjects are considered as having received both treatments if they received each treatment at least once.
- Pool 3: Comprising 16 non-controlled studies (N=6,596)  
This pool includes 4 non-controlled extension studies. For these extension studies, incidence rates were calculated based on the number of subjects entering the extension studies.
- Pool 4: Comprising all 62 studies included in GIAD (= total vardenafil experience), e.g., 50 IR (Levitra) and 2 ODT (Staxyn) studies (N=17,952 vardenafil)

Bayer noted that 3 studies were placebo as well as active-controlled and were therefore included in both Pool 1 and Pool 2. There were no ocular melanomas noted in the entire clinical trial experience. All further discussion refers to skin melanomas.

1. In placebo-controlled studies (Pool 1), there are no subjects with melanoma (including ocular melanoma) at all (0/9,359 vardenafil, 0/5,706 placebo). In active-controlled studies (Pool 2), there are no subjects (0/2360 active comparator, 0/2598 vardenafil) with melanoma (including ocular melanoma).
2. Tables 20-22 shows all the Sponsor's analysis using Pool 4, comprising all 62 studies included in the GIAD (= total vardenafil experience), e.g., 50 immediate release (IR) Levitra and 2 orally disintegrating (ODT) Staxyn studies (N=17,952 vardenafil).

**Table 20: Subjects with Melanoma AEs by Vardenafil Dose in the Bayer Global Integrated Analysis Database (GIAD Pool 4)**

Preferred Term	Vardenafil				
	2.5 mg n=173	5 mg n=674	10 mg n=5577	20 mg n=4585	Flex dose* n=6943
Malignant Melanoma	0	0	1 (0.018%)	1 (0.22%)	1 (0.014%)

\* All subjects who received at least 2 different doses are summarized under vardenafil flex dose for the purpose of this analysis, including vardenafil unknown dose, 10mg, 20 mg, vardenafil od (once daily), vardenafil od → vardenafil, vardenafil forced titration, and vardenafil flex dose.

Source: Table 1 of Sponsor's IR Response, page 9.

**Table 21: Number of Subjects with Melanoma AE by Vardenafil Treatment Duration in the Bayer Global Integrated Analysis Database (GIAD Pool 4)**

Preferred Term	Treatment Duration					
	Missing n=4	≤3 months n=12,684	3-6 months n=2665	6 mos-1 yr n=1986	1-1.5 yrs n=92	>1.5 yrs n=521
Malignant Melanoma	0	0	0	1 (0.050%)	1 (1.087%)	1 (0.192%)

Source: Table 2 of Sponsor's IR Response, page 9.

**Table 22: Number of Subjects with Melanoma AE by Relative Days from Treatment Start to AE Start in the Bayer Global Integrated Analysis Database (GIAD Pool 4)**

Preferred Term	Relative Days from Start of AE to Start of Treatment	Vardenafil N=17,955
Malignant Melanoma	≤14 days	0
	15 days-≤ 1 month (30 days)	0
	31 days-≤6 months (180 days)	0
	181 days-≤year (360 days)	1 (0.006%)
	>360 days	2 (0.0011%)
	Total	3 (0.017%)

Source: Table 3 of Sponsor's IR Response, page 10.

*Reviewer's Comment: Two of the three vardenafil-treated melanoma patients had been previously treated with sildenafil.*

*Reviewer's Comment: With these low melanoma incidence rates, the requested analyses comparing vardenafil to placebo, and assessing incidence rates by dose, duration, and length of time from vardenafil exposure to start of AE do not reveal any meaningful findings. There is no indication of a dose response. In addition, there is no indication that vardenafil is a melanoma growth promoter.*

3. For their Analysis 3, Bayer did a comparison of melanoma AE incidence rates between daily use and ad lib use. This analysis was based also on Pool 4 – the GIAD.

**Table 23: Melanoma AE by Daily Vs. PRN Treatment Group in the Bayer Global Integrated Analysis Database (GIAD Pool 4)**

Preferred Term	Vardenafil Dosing Groups		
	OD n=456	BID n=129	PRN n=17,367
Malignant Melanoma	0	0	3 (0.17%)

Source: Table 7 of Sponsor's IR Response, page 13

*Reviewer's Comment: The numbers of subjects with daily dosing of vardenafil are too low to allow for any trend conclusions.*

4. For their Analysis 4, Bayer conducted an analysis of melanoma AEs from their uncontrolled vardenafil studies. In the subset of 16 non-controlled studies (n=6,596), there were 3 subjects with melanoma who received vardenafil (3/6596 [0.1%]). The overall incidence rates of melanoma among all male and white male patients exposed to vardenafil (using Pool 4) were lower than the reported SEER incidence rates for all ages except for Whites, aged 45-54 years. In the two age groups encompassed by this age span, the incidence rates were higher in the vardenafil non-controlled studies than the SEER incidence rates. In the subset of patients included in non-controlled clinical trials (Pool 3), the incidence rates of melanoma were higher than expected based on SEER incidence rates for all ages, but in the high risk age categories (60-85+) there were 0/6104 melanoma cases for Pool 4 and 0/2156 melanoma cases for Pool 3.

**Table 24: Melanoma Age Adjusted AE Reporting Rates for Non-Controlled Vardenafil Studies vs the Total Vardenafil Population vs SEER Incidence Rates**

Patient Age at Diagnosis (selected brackets)	SEER Incidences 2009-2013	GIAD Total (Pool 4)	GIAD Non-controlled (Pool 3)
	All males or White Males Rate per 100.000		
All Ages	All: 28.5 White: 33.3	All: 16.7 (3/17952) White: 23.8(3/12596)	All: 45.5 (3/6596) White: 56.3(3/5325)
Age Brackets Where Seer Rates Were Exceeded			
45-49	All: 20.9 White: 25.4	All: 45.9 (1/2178) White: 70.9(1/1410)	All: 119.5 (1/837) White: 149.3(1/670)
50-54	All: 33.0 White: 39.2	All: 32.7 (1/3054) White: 47.2 (1/2109)	All: 88.3 (1/1132) White: 109.4 (1/914)
55-59	All: 45.5 White: 53.5	All: 27.5 (1/3633) White: 37.3 (1/2683)	All: 72.7 (1/1375) White: 88.7 (1/1127)
No Incidence of Melanoma in these High Risk Age Brackets			
60-85+		All: 6104 (0/6104) White: 4605 (0/4605)	All: 2156 (0/2156) White: 1784 (0/1784)

Source: Table 9 of Sponsor's IR Response, page 16

*Reviewer's Comment: The above analysis is dependent on 3 cases of melanoma two of which had been pre-treated with sildenafil. There is an absence of melanoma among high risk patients (age >65 years). With this small number of melanoma AEs, and no cases in the highest risk age category, it is difficult to make any statement about a trend.*

5. Bayer calculated that a relative risk of melanoma by use of other PDE5i compared to no use of other PDE5i. That RR was 3.123 with a 95% CI (RR) of [0.403; 42.374 which includes 1.0]. In Pool 4, the incidence of melanoma in subjects that had received no previous or concomitant PDE5i was 0.009% (1/10943). The incidence of melanoma in patients that had received previous or concomitant PDE5i was 0.029% (2/7009). In the patient who developed melanoma without prior/other PDE5i exposure, the lesion occurred at greater than 360 days after exposure to vardenafil. Of the 2 patients with previous exposure to other PDE5i, one lesion occurred after 360 days following vardenafil exposure and one lesion occurred between 181 and 360 days following

varденафил exposure. No melanomas occurred in daily vardenafil use patients regardless of previous PDE5i use status.

*Reviewer's Comment: The above analysis is dependent on 3 patients with an AE of melanoma, two of which had been previously with sildenafil. With this small number of melanoma AEs, it is difficult to make any statement about a trend.*

6. To address Analysis #6, Bayer identified the following risk factors: age  $\geq 60$  years, Caucasian race, and the following skin lesions: precancerous, xeroderma pigmentosum, actinic keratosis, dysplastic nevus, congenital melanocytic nevus, tanning and heavy ultraviolet light exposure. Pool 4 was used for the analysis. The number of subjects with any of the above risk factors is shown in the table below:

**Table 25: Subjects with Risk Factors in Medical History**

<b>Age</b>	
<60 years	11,827 (66.1%)
$\geq 60$ years	6,069 (33.9%)
<b>Race</b>	
Other	5,356 (29.9%)
White	12,540 (70.1%)
<b>Age and Race</b>	
<60 years and other	3,857 (21.6%)
$\geq 60$ years or white	14,039 (78.4%)
<b>Treatment group (varденафил dose)</b>	
2.5 mg	173 (1.0%)
5 mg	672 (3.8%)
10mg	672 (3.8%)
20 mg	4,566,913 (38.6%) 8 (25.5%)
flexible dose	

*Source: Table 20 of Sponsor's IR Response, page 26*

All 3 subjects with melanoma are of White race; therefore, there are no melanoma cases in the "no risk factor group." The Sponsor has then recalculated melanoma incidence for risk factors included and excluded relative to drug dose, treatment duration and time to onset following vardenafil therapy. The incidence results were minimally higher for these analyses. The incidence of melanoma for any risk factor was 3/14095 (0.021%) versus 0/3857 for patients with no risk factors.

*Reviewer's Comment: This analysis did not add any new information, in my opinion.*

7. In the overall evaluation of data (Analysis 8), Bayer stated that owing to the low melanoma incidence rates, the requested analyses did not reveal any meaningful findings. The overall incidence rates of melanoma among patients exposed to vardenafil was lower than the reported SEER melanoma incidence rates except for 2 of the three age groups in which cases of melanoma were seen (but not higher than SEER

incidence rate in the highest risk age category). Due to the low number of melanoma cases observed as well as the absence of melanoma among high risk patients (age>65 years), the meaningfulness of these findings is questionable.

*Reviewer's Comment: We agree with Bayer's overall conclusion.*

Bayer's analysis of basal cell carcinoma (BCC) AEs from the vardenafil clinical studies is provided below:

For Analysis 1, in placebo-controlled studies, there 3 subjects with a basal cell carcinoma (BCC) AE, as follows: 2/9359 [0.021%] vardenafil versus 1/5706 [0.018%] placebo. In active control studies, there were no occurrences of BCC.

For Analysis 2, in placebo-controlled studies, there were 2 subjects with BCC under vardenafil treatment, Subject 1 (1/207) had been treated with vardenafil flexible dose once daily (od), while Subject 2 (1/2922) had been treated with vardenafil 10 mg and then switched to vardenafil flexible dose, e.g., from 10 mg to 20 mg, after 33 days. The time from the first vardenafil dose to the start of AE was 256 days for Subject 1 and approximately 80 days (incomplete date) for Subject 2. One subject with basal cell cancer was treated with placebo. The time from the first placebo dose to the start of AE was 13 days. There were no cases of BCC in active-controlled studies. There does not appear to be a dose response for BCC in response to vardenafil therapy. There appears to be no indication of a response of BCC to vardenafil treatment duration. The time to onset to BCC while on vardenafil is earlier than the time to onset for melanoma while on vardenafil.

For Analysis 3, in Pool 4, the incidence of BCC in once daily vardenafil dosed patients exceeds that of prn dosed patients, but is based on 1 case only. No bid dosed patient developed BCC. The numbers of daily dosed patients are small. Based upon the small numbers of daily dosed vardenafil patients a meaningful comparison cannot be made. These results do not support the observed increase in BCC with daily use of vardenafil.

In Analysis 4, Bayer stated that there are no SEER data for BCC in the US.

In Analysis 5, in Pools 1 and 5, 5/8 BCC subjects received sildenafil prior to study start (4/7 vardenafil and 1/1 placebo). In Pool 4, 3/10943 (0.46%) of no other PDE5i exposure subjects had BCC versus 4/7009 (0.057%) of patients who reported use of other PDE5i medications. The times of onset did not appear significantly different based upon previous PDE5i exposure status. These BCC cases appeared in the 10 -20 mg vardenafil dose groups. The subject numbers are too small to provide meaningful data for BCC incidence in daily vardenafil dosed subjects previously exposed to PDE5i medication.

In Analysis 6, all BCC patients were Caucasian: therefore, all BCC patient did have a melanoma risk factor. Using Pool 4, the incidence of BCC in the 3857 subjects with no risk factor was 0/3857. The incidence of BCC in 14095 subjects with any risk factor was 0.05% (7/14095).

Bayer states that the overall analyses for BCC did not elicit meaningful findings. The Sponsor observes that most cases of melanoma and BCC had a history of PDE5i use before entering the study. The Sponsor believes that this fact supports the finding noted in previous epidemiology studies that PDE5i users may have an increased risk of melanoma and BCC due to a different life style with higher sun exposure and melanoma is not caused by PDE5i use.

*Reviewer's Comment: We agree with Bayer's overall conclusion.*

#### 4.5.3 Lilly: Tadalafil

Lilly responded to the information request August 11, 2016. The tadalafil clinical trial database was searched cumulatively through 15 June 2016 for cases of treatment-emergent skin and ocular melanoma, and basal cell carcinoma. The searches were conducted using MedDRA, Version 19.0. All data from completed clinical trials of tadalafil in the treatment of ED or BPH were searched. The preferred terms (PTs) utilized for the search are as follows:

- Melanoma – all PTs under the high level terms (HLT) of ‘Skin melanomas (excluding ocular)’ and ‘Ocular melanomas’
- Basal cell carcinoma – PT ‘basal cell carcinoma’.

An event was considered treatment-emergent if the event was first reported, or worsened in severity, after randomization, or initiation of open-label treatment. Results were summarized for the overall population as well as separately by dosing regimen to minimize potential bias introduced by pooling of heterogeneous populations. Within the tadalafil ED and BPH development programs, on-demand treatment (PRN; as needed) dosing was only examined within ED patients (while a once daily [QD] dosing regimen was examined in both ED and BPH).

The search in the clinical trial database utilizing the HLTs for skin and ocular melanoma identified a total of 4 tadalafil-treated patients with AEs of skin melanoma. There were no placebo patients with melanoma AEs. The search also identified 6 tadalafil-treated patients with events of basal cell carcinoma (BCC) and 2 placebo patients with BCC. One patient had an event of BCC while treated on placebo and an additional event while treated with tadalafil. There were no cases of ocular melanoma in the clinical trial database. For all cancers evaluated, no statistically significant difference in incidence rates was observed between placebo and tadalafil as all confidence intervals contained 0.

**Table 26: Melanoma and Basal Cell Carcinoma TEAEs across All Tadalafil ED and BPH Studies by Dosing Regimen**

Dosing Regimen	Subjects with TEAE/ Number of Subjects	Incidence Rate (%)	Incidence Rate (95% CI)
<b>Melanoma</b>			
PRN	2/17457	0.01 %	(0.00, 0.04)
QD	2/6710	0.03%	(0.00, 0.11)
Overall	4/24148	0.02%	(0.00, 0.04)
<b>Basal Cell Carcinoma</b>			
PRN	3/17457	0.02%	(0.00, 0.05)
QD	3/6710	0.04%	(0.01, 0.13)
Overall	6/24148	0.02%	(0.01, 0.05)

Source: Table 5.3 of submission, page 14

Lilly provided the following responses to the Analysis questions for melanoma AEs:

1. For Analysis 1: There were 2 cases of melanoma in the ED PRN indication. There were no cases in placebo-controlled QD trials of ED or BPH.

**Table 27: Melanoma and Basal Cell Carcinoma TEAES in Double-Blind Tadalafil Studies by Dosing Regimen**

Dosing Regimen	Placebo			Tadalafil			Treatment Difference	
	Cases/ Total subjects	IR (%)	Incidence per PY	Cases/ Total subjects	IR (%)	Incidence per PY	IR (95% CI)	RR (95% CI)
<b>Melanoma</b>								
PRN	0 /1982	0%	0	2 /4730	0.04%	1.788	0.04 (-0.02, 0.10)	NA
QD	0 /3086	0%	0	5 /5475	0%	0	NA	NA
Overall	0 /5209	0%	0	2 /10205	0.02%	0.824	0.02 (-0.01, 0.05)	NA
<b>Basal Cell Carcinoma</b>								
PRN	1 /1822	0.05%	2.354	0 /4730	0%	0	0.05 (-0.15, 0.05)	NA
QD	1 /3086	0.05%	1.635	1 /5475	0.02%	0.764	-0.01 (-0.09, 0.06)	0.560 (0.035, 8.955)
Overall	2 /5209	0.04%	1.601	1 /10205	0.01%	0.412	-0.03 (-0.09, 0.03)	0.257 (0.023, 2.839)

Source: Table 5.1 of submission, page 11; NA=data not available

*Reviewer's Comment: This comparison does not indicate a significant indication for causal association or for tumor growth promotion for Cialis and melanoma.*

2. For Analysis 2: There were only 4 cases of melanoma to be analyzed by dose, duration, and length of time from tadalafil exposure. There is a fifth patient who had pre-existing melanoma. This patient is not considered as the case was classified as being not treatment emergent.

**Table 28: Clinical Trial Melanoma Cases**

Patient Age	Indication for use	Dose at Time of Event	Time to Onset of Event (days)	Study Type
50	ED	5 mg QD	100	Double Blind
63	ED	20 mg PRN	43	Double Blind
79	ED	20 mg PRN	7	Double Blind
82	ED/BPH	5 mg QD	134	Open Label Extension

Source: Table 5.4 of submission, page 15

*Reviewer's Comment: The number of cases is too small to allow any meaningful conclusions for this analysis.*

3. For Analysis 3: This analysis compares melanoma incidence rates between daily use and prn use of tadalafil in double-blind studies. The reader is referred to Table 27. The incidence of melanoma AEs is higher in the prn group than in the once daily group. The time to onset from start of therapy to the AE is also longer in the once daily group than it is in the prn group. Table 29 below summarizes incidence rates in open-label studies.

*Reviewer's Comment: The above result does not support a cumulative exposure effect for tadalafil, but the numbers are quite small.*

The following table provides incidences rates or melanoma and BC AEs in open-label tadalafil studies.

**Table 29: Incidence Rates of Melanoma and Basal Cell Cancer AEs in Open-Label Tadalafil Studies**

Dosing Regimen	Case Number/Total Population	Incidence Rate (%)	Incidence Rate (95% CI)
<b>Melanoma</b>			
PRN	0 /9372	0%	(0.00-0.03)**
PRN (age>=50)	0 /6787	0%	(0.00-0.04)**
QD	1 /2429	0.04%	(0.00-0.26)
QD (age >=50)	1 /2028	0.05%	(0.00-0.27)
Overall	1 /12142	0.01%	(0.00-0.10)
Overall (age >=50)	1 /8824	0.01%	(0.00-0.06)
<b>Basal Cell Carcinoma</b>			
PRN	3 /9732	0.03%	(0.01-0.09)
PRN (age>=50)	3 /6787	0.04 %	(0.01-0.13)
QD	2 /2429	0.08%	(0.01-0.30)
QD (age >=50)	2 /2028	0.10%	(0.01-0.36)
Overall	5 /12142	0.04%	(0.01-0.10)
Overall (age >=50)	5 /8842	0.6 %	(0.02-0.13)

Source: Table 5.2 of October 14, 2016 submission (Seq 0110) which corrected an error in Table 5.2 in the original submission; \*\* CI calculated using the 3 over N rule

*Reviewer's Comment: The open label data do not support a statistically significant effect for tadalafil and melanoma. The results relative to basal cell cancer argue against a causal or growth promoting role for tadalafil and melanoma.*

4. For Analysis 4: Results in uncontrolled studies compared to SEER results. In SEER, the overall age-adjusted incidence rate of melanoma was 23.77/100,000 (0.02%) in 2013. Specifically, the age-adjusted incidence rate of melanoma among Caucasian men aged 50 years and older was 110.03/100,000 (0.1%) in 2013. There was only 1 melanoma case in an open-label study of ED or BPH. The overall incidence rates of melanoma from these studies are similar to the rates described in SEER. In open-label studies, the overall rate of melanoma was 0.02% for under and over 50 years of age.
5. For Analysis 5: There were no cases in which more than one PDE5i was used by the same subject at the same time or separately for either basal cell cancer or melanoma.
6. For Analysis 6: Cases in which melanoma risk factors were present. Table 28 identifies all 4 melanoma cases as  $\geq 50$  years of age. All melanoma subjects including the non-treatment emergent melanoma case were Caucasian.

The Sponsor's conclusion for tadalafil and melanoma are combined and shown below. The Sponsor believes that the evidence does not show an effect of tadalafil on melanoma or BCC.

Lilly provided the following responses to the Analysis questions for basal cell cancer (BCC) AEs:

1. The Sponsor provided a comparison of incidence rates for BCC for placebo and Cialis
2. The Sponsor provided BCC incidence rates by dose, duration and length

**Table 27: Basal Cell Cancer Cases in Tadalafil Clinical Trials**

Age	Indication for Use	Dose at Event Time	Dose Frequency	Time to Onset(days)	Risk Factors	Trial Type: Comments
65	ED	2.5 mg	PRN	459	Caucasian	Open label extension
70	ED	20 mg	PRN	204	Caucasian	Open label extension
73*	ED	Placebo	PRN	63	Caucasian: previous skin neoplasm x2	Double-blind/ Open label extension
65	ED/BPH	5 mg	QD	51	Caucasian: Previous basal cell carcinoma	Open label extension
80	ED/BPH	5 mg	QD	208	Caucasian	Open label extension
63	ED/BPH	Placebo	QD	5	Caucasian	Double-blind
75	ED/BPH	5 mg	QD	77	Caucasian	Double-blind

*\*This patient experienced basal cell carcinoma while on placebo. The lesion was removed prior to completing the study. The patient enrolled in an open label extension and in the baseline study period, the BCC was not present. In the open label extension after dosing with tadalafil 20 mg, patient experienced onset of a new basal cell carcinoma. Source: Table 5.6 of submission, page 17.*

*Reviewer's Comment: Two patients had had previous basal cell carcinomas. One was a placebo subject and one was a 5 mg one daily tadalafil subject. Eliminating both patients yields an overall incidence rate for basal cell carcinoma of 0.09% (5/5558 [95%CI (0.03-0.21)] versus 0 for placebo. This positive result for a negative control argues against a causal role or growth promotional role for tadalafil and melanoma in the time periods covered by these studies.*

3. To compare BCC incidence rates between tadalafil daily use and tadalafil prn use, the reader is referred to the previous tables. In the double-blind, placebo controlled studies, no statistically significant incidence rate differences were noted. In open-label studies, (see previous table) there was an increase in BCC AEs in tadalafil subjects and there was not an increase for melanoma. Across all ED and BPH studies (see previous table), there was there was an increase in BCC AEs in once daily tadalafil subjects only and there was not an increase for melanoma in any category.

*Reviewers Comment: This result for a negative control argues against a causal role or growth promotional role for tadalafil and melanoma in the time periods covered by these studies.*

4. In comparing basal cell carcinoma incidence rates to demographically matched SEER rates, it is noted that data for basal cell carcinomas are not tracked by cancer registries. Among men aged 40-75 years of age in the United States, the age-adjusted incidence rate of BCC ranged from 606-1488 cases per 100,000 person years. The incidence rates of BCC in tadalafil open label studies of ED and BPH were lower than rates described in the literature. The reader is referred to previous tables.
5. There were no cases in which more than one PDE5i was used by the same subject at the same time or separately for either BCC or melanoma.
6. Baseline risk factors for BCC were reported in all cases of BCC. The reader is referred to Table 5.6. All patients were Caucasian and over 65 years of age. Two of the patients had had previous basal cell carcinomas.

The Sponsor's overall conclusions are that for all cancers evaluated, no statistically significant difference in melanoma incidence rates was observed between placebo and tadalafil in the clinical trial database. In the open-label extension (OLE) trials the incidence rates of melanoma were similar to the SEER age-adjusted incidence rate of melanoma among Caucasian men aged 50 years and older (0.1%) and the SEER overall age-adjusted incidence rate of melanoma (0.02%) in 2013. For basal cell carcinoma in OLE trials, the incidence rates were lower than the range of 606 – 1,488 cases per 100,000 person years reported in the literature.

Based upon totality of evidence from all currently available data sources, Lilly concludes that there is no causal association between tadalafil exposure and melanoma or basal cell carcinoma.

*Reviewer's Comment: I concur with Sponsor's evaluation and conclusion.*

*Reviewer's Overall Comment on Sponsor's Responses to FDA Information Requests: Clinical trial and PDE5i Sponsor postmarketing data overall do not suggest a melanoma signal.*

## 5. Office of Pharmacovigilance and Epidemiology Review

DPV-II identified 203 cases of melanoma in patients receiving a PDE5i, of which 190 reported use of sildenafil. A total of 93 out of 95 cases with a documented reason for use reported erectile dysfunction as the indication. Despite chronic and more frequent dosing, we only identified one case reporting melanoma in situ in a female patient on PDE5i for pulmonary arterial hypertension (PAH). Because of a lack of documented PDE5i dose information in the case series, DPV-II was unable to comment on a dose-response relationship. Furthermore, the cases lacked documentation of melanoma risk factors such as genetic and lifestyle factors that may play a role in the onset of melanoma. It was noted a large proportion of the 203 cases were reported by lawyers (n=174) and by consumers (n=5) in response to class action lawsuits soon after the Li *et al.* publication.

Considering the intermittent (and therefore inconsistent) exposure of PDE5i in the treatment of ED, the long onset latency of melanoma, and insufficient data quality in the FAERS cases, DPV-II is unable to draw any causal inference from their analysis.

## 6. Oncology Consultation

The Division of Oncology Products (DOP) was asked to conduct a consultation and to provide an oncologic opinion for the information relating to melanoma AEs and Viagra and the other PDE5i. In their completed consult November 28, 2016, the DOP conclusion was as follows:

*“Despite a potential plausible biological mechanism, there is no data to support a causal role for sildenafil for increased risk of melanoma. The clinical relevance of the studies is not clear. All the approved PDE5Is were not carcinogenic in animal studies”*

The Oncology consultation further stated that in the placebo-controlled and active-controlled clinical studies of PDE5Is, based on the information provided by the Sponsors, no obvious imbalance in melanoma and basal cell carcinoma was noted. Although all the patients were Caucasians of older age and male gender, there was insufficient information on other risk factors for melanoma. The median age was 69 years (range: 45-82), which is higher than the reported median age at time of diagnosis of melanoma which is 59 years in the general population. There was a wide variance in the dose and duration of the drugs. The small number of cases did not provide any clinically meaningful differences as the calculation and interpretation of incidence rates and relative risk were limited. However, the occurrence of melanoma is low, which could leave a genuine risk undetected.

The Oncology consultation also stated that post marketing reports contained insufficient information for a meaningful clinical assessment to determine the association of melanoma with

PDE5I use, particularly with reference to risk factors for melanoma, medical history, concomitant medications, dose and schedule of treatment, duration of treatment, preponderance of specific anatomic sites, and the presence of mutations in melanoma. There are ongoing lawsuits that would facilitate reporting bias.

In conclusion, based upon the information provided and the currently available data sources, the Oncology consultation concluded that there is no definitive signal from the clinical oncology perspective that suggests a causal relationship between administration of PDE5Is and melanoma.

## 7. Pharmacology Toxicology Review

The Pharmacology/Toxicology memorandum was completed March 29, 2017. The Pharmacology/Toxicology review team concluded:

“There is no definitive evidence indicating that PDE5i could promote melanoma development in human melanoma cells. It is unknown if these drugs would directly bind to melanin or enter a melanocyte or modulate melanogenesis during melanin synthesis in human melanoma cells. In the reviewer’s view, the effect of PDE5i on melanin (eumelanin and pheomelanin) content and cell viability in human melanocytes and melanin-containing tissues should at least be assessed at clinically relevant concentrations. Binding to melanocortin-1 receptor, the major regulator of melanogenesis would provide a potential role for PDE5i in melanin synthesis. Additional studies assessing the effect of PDE5i on melanoma proliferation in human primary and metastatic melanoma cells and/or in vivo melanoma model (e.g., patient-derived xenograft) with wild type comparing the BRAF mutation may provide further insights into the drug’s role, if any, in melanoma development.”

In an April 5, 2017, Pharmacology/Toxicology Memorandum, for clarification, it is stated

“...the Nonclinical Team does not recommend new nonclinical studies and pharmacovigilance is the most appropriate method to monitor potential melanoma development in PDE 5 inhibitor users.” The recommended “...above studies would provide further insights into the PDE5 inhibitor role, if any, in melanoma development; but may not provide a causal link as there are currently too many variables to define the role of PDE5 inhibitors in melanoma formation.”

## 8. Reviewer’s Overall Conclusion

The data from the original FAERS cases do not show:

- The incidence of melanoma continuing long after the drug was discontinued
- A clinical indication that sildenafil or any PDE5i is a growth promoter.
- Adequate documentation of cumulative patient exposure experienced at the time of melanoma occurrence.
- Person time exposure (available in only 28 patients) to melanoma occurrence.
- Characterization of actual patient PDE5i use.

- Adequate documentation of melanoma occurrence in sufficient numbers after 10-15 years of use.

At the current time the data are insufficient to draw a conclusion that there is a causal association between Viagra or any PDE5i and the occurrence of melanoma.

## **9. Recommended Regulatory Action**

The recommended regulatory action at this time is continued pharmacovigilance.

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/s/  
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A R WIEDERHORN  
07/12/2017

MARK S HIRSCH  
07/12/2017  
I concur.